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Topics in the Surgery of the Biliary Tree

Edited by Hesham Abdeldayem

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Meet the editor

Professor Abdeldayem graduated from the Kasr Al-Ainy Faculty of Medicine, Cairo University, in 1987. He got his training at the Cairo University Hospitals, National Liver Institute, Ysbyty Gwynedd, Bronglais General Hospital, General Hospital Ayr, University of Pittsburgh Medical Center, and King Abdulaziz Medical City. He joined the National Liver Institute in 1993. He has several publications in the field of hepatopancreatobiliary surgery and organ transplantation. He currently holds the positions as a professor of Surgery and the dean at the National Liver Institute, Menoufia University, Egypt.

Contents

Preface

Biliary tree diseases are prevalent worldwide. They result in a considerable amount of financial and social burden. At the same time, clinical studies on these diseases continue to advance at a rapid pace.

The articles in this book provide state-of-the-art reviews on the current knowledge and advances in research and management of biliary tree diseases. It includes the most recent advances in that field, particularly cholangiocarcinoma, biliary tree injuries, and biliary cysts.

This book is written by recognized medical experts and researchers. I would like to thank all the distinguished authors for their cooperation and desire to share their precious experience with the medical community. On their behalf, I wish to express hope that this publication will facilitate access to the latest scientific achievements in the field of surgery of the biliary tree diseases all around the world.

I am particularly thankful to Mr. Markus Mattila and his colleagues at IntechOpen, the publisher of one of the largest multidisciplinary open-access collections of books covering the field of science, for their expertise and support in bringing this edition to completion.

I would like to acknowledge the help of my colleagues at the National Liver Institute, Menoufia University, Egypt, a dedicated center of excellence and a leading medical institution at the Middle East involved in the management of liver diseases and advanced training and research in hepatobiliary sciences.

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Introduction

Chapter 1

Introductory Chapter: Biliary Tree

Hesham Abdeldayem

Additional information is available at the end of the chapter

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1. The biliary tree

Bile flows through canaliculi formed by the walls of the hepatocytes, then into successively larger ducts: the term biliary tree is derived from the arboreal branches of the bile ducts. The liver produces 500–1000 mL of bile per day. The bile ducts, gallbladder, and sphincter of Oddi modify, store, and regulate the bile flow [1].

2. Biliary stones

Biliary stones are formed as a result of failure to maintain biliary solutes (primarily, cholesterol and calcium salts) in a soluble state. The pathogenesis is multifactorial and involves cholesterol supersaturation, crystal nucleation, and gallbladder dysmotility. The vast majority of patients are asymptomatic, often discovered at laparotomy or during abdominal imaging. Over time, asymptomatic gallstones can progress to symptomatic disease. Prophylactic cholecystectomy is not generally indicated in patients with asymptomatic gallstones. Prophylactic cholecystectomy is considered for children with gallstones, patients with sickle cell disease (as cholecystitis can precipitate a crisis with substantial operative risks), and large gallstones (>2.5 cm), porcelain gallbladder (calcified gallbladder wall). Acute cholecystitis results from a stone impaction at the gallbladder-cystic duct junction. The extent and the progression of inflammation are related to the duration and degree of obstruction. In severe cases, this process can lead to ischemia and necrosis of the gallbladder wall. More frequently, the gallstone is dislodged, and the inflammation gradually resolves. Intrahepatic stones are more prevalent in Asia. They are associated with prolonged partial BD obstruction, as in sclerosing cholangitis, benign and malignant biliary strictures, choledochal cysts, and biliary parasites. Mirizzi syndrome is a form of obstructive jaundice, first described by Mirizzi in 1948, caused

by a stone or stones impacted in the neck of the gallbladder or the cystic duct, such that the common hepatic duct (CHD) is narrowed. It occurs in about 0.1–0.7% of patients who have gallstones [2].

Gallstone ileus results from fistula formation from the biliary tract to the intestine. It is mainly a disease of the elderly and of women. The advanced age and medical comorbidities contribute to the high morbidity and mortality. Clinical suspicion for this entity must exist. It is often a consequence of inflammation of the gallbladder, adhesions to adjacent bowel, with subsequent pressure and ischemia causing a gallstone to erode into the bowel, resulting in fistula formation. Most of the stones pass without consequence. Obstruction occurs if the stone is of large enough size, mostly bigger, greater than 2–2.5 cm. The point of obstruction is most often in the terminal ileum because of its smaller diameter, but it can occur throughout the GI system [3].

3. Biliary strictures

Biliary strictures are usually caused by inflammatory conditions such as chronic pancreatitis, cholelithiasis and choledocholithiasis, primary sclerosing cholangitis, stenosis of the sphincter of Oddi, duodenal ulcer, and Crohn's disease. Drugs follow injury at a primary biliary operations as laparoscopic cholecystectomy. Strictures also can complicate open cholecystectomy, common bile duct exploration, gastrectomy, and hepatic resection. Ischemia of the bile duct, unnecessary dissection around the bile duct during cholecystectomy or bile duct anastomosis can divide or injure the major arteries of the bile duct that run in the 3 o'clock and 9 o'clock positions. Marked local inflammatory response can develop in association with bile leakage, which occurs with many bile duct injuries. This results in fibrosis and scarring in the periductal tissue, contributing to stricture formation [4].

4. Biliary fistulas

Biliary fistulas are classified by the etiology as spontaneous, posttraumatic, iatrogenic, or postoperative. They can be classified by the site of exit as internal fistulas (the most frequent site is to the GI tract, particularly the duodenum) and external (commonly postoperative) [4].

5. Cholangiocarcinoma

Cholangiocarcinoma is defined as primary malignancy originating from BD epithelium. It is the second most common primary hepatic neoplasia. These cancers tend to grow perpendicularly to, and horizontally along, the bile duct, and therefore, tumors that are detected by imaging tend to be underestimated. The anatomic relationship of the distal bile duct to the pancreas, duodenum, portal vein, and hepatic artery can also make removal of these tumors

technically challenging. Although these tumors can occur at any level of the biliary tree, nearly two-thirds occur at the bifurcation of the bile duct (hilar cholangiocarcinoma), where they are often referred to as Klatskin tumors. Surgery remains the primary curative modality. Most cases cannot undergo curative resection because of patient-related causes (medical comorbidities), local anatomic causes (local tumor extension), and tumor biology (metastatic disease). Three main subgroups are (1) hilar tumors involving the confluence of the left and right HDs and the CHD, (2) mid-duct tumors involving the supraduodenal CBD, and (3) distal involving the intraduodenal bile duct. This classification is based upon on the technique required for curative resection. Hilar tumors require excision of the CHD and frequently concomitant hepatic parenchymal resections; mid-duct tumors rarely require concomitant hepatic resections; distal tumors necessitate pancreaticoduodenectomy [4].

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Cholangiocarcinoma

Chapter 2

Intrahepatic Cholangiocarcinoma

Marco Massani, Tommaso Stecca, Bruno Pauletti, Gianpaolo Marte, Cesare Ruffolo, Luca Bonariol and Nicolo' Bassi

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Abstract

Aim: The authors give a complete overview on this disease from epidemiology to treatment.

Background: Cholangiocarcinoma (CCA) is an epithelial tumor with features of cholangiocyte differentiation. Most patients suffer from a nonresectable disease since presentation and the exitus occurs within 12 months from diagnosis. Biliary epithelial carcinogenesis is a multistep process that involves the transition from hyperplasia to dysplasia to carcinoma. The clinical approach should be multidisciplinary, and the diagnosis should be considered when there is a histological finding of adenocarcinoma without any other evidences of an extrahepatic primitive neoplasia. Surgical resection with histologically negative margins is the only curative treatment. Nevertheless for unresectable patients, there are several other approaches: systemic chemotherapy is the widely used treatment, but a large proportion of patients could be suitable for liver-directed therapies. These options include transarterial chemoembolization (TACE), radioembolization (TARE), hepatic arterial infusion (HAI), percutaneous ablation, and external beam radiation therapy (EBRT).

Conclusion: Intrahepatic cholangiocarcinoma is a relatively rare disease with a poor prognosis. Diagnosis is based on imaging, but pathological anatomy plays an important role. Surgery is still the gold standard treatment; nevertheless, unresectable patients could be treated in a multimodality strategy with a significant improvement in terms of survival.

Keywords: cholangiocarcinoma, chemotherapy, surgery

1. Introduction

The first description of a case of cholangiocarcinoma dates from 1840 on the merits of Durand-Fardel. Cholangiocarcinoma (CCA) is an epithelial tumor with features of

cholangiocyte differentiation [1]. It originates from the ductal epithelium of the biliary tree from the canals of Hering to the main bile duct [2]. This pathology is sordid, difficult to diagnose, and is generally fatal because of late clinical presentation and lack of effective alternative therapeutic approaches to surgery. Most patients suffer from a nonresectable disease since presentation and the exitus occurs within 12 months from diagnosis for the effects of cachexia and rapid decline in performance status. Liver failure, recurrent sepsis, and secondary biliary obstruction can also contribute to the high mortality [3]. The overall survival rate, including patients undergoing surgery, is low, with less than 5% of patients alive at 5 years. Although cholangiocarcinoma is a relatively rare disease, the interest of the scientific community has increased in recent years also due to the augmented incidence of the intrahepatic variant [3].

2. Epidemiology

CCA represents 3% of all gastrointestinal tumors and is the second most common primitive liver cancer. The incidence peak is reached in the seventh decade and is slightly more frequent in the male with a ratio of 1.5:1 [4]. The rates of incidence are characterized by an enormous geographical variation reflecting the distribution of local environmental risk factors in addition to the genetic differences between the various populations [5, 6]. The increase in incidence rates along with mortality rates has been documented worldwide: Europe and North America, Japan, and Australia [3]. Consistent with the data from US registers [7], the AISF "Cholangiocarcinoma" committee reported comprehensive national data from Italian National Cancer Registries of the period between 1988 and 2002. A consistently increasing trend was observed for iCCA: from 5 to 12 cases per million (average increase = 6% per year) [8]. In the United Kingdom, since the 1990s, the iCCA exceeded hepatocellular carcinoma as the leading cause of death among primitive liver tumors [9].

3. Prognosis

The overall prognosis is poor with a 5-year survival rate of less than 5%. The median survival for iCCA is between 18 and 30 months, but if not resectable it decreases to 6 months. The only curative therapeutic option may be expected from liver resection for tumors at the initial stage, after which 5-year survival rate varies from 20 to 40% [10]. However, as most patients present with an advanced disease, thus precluding the surgical option, 75% of patients die between the first year from diagnosis [11]. Cancer cachexia, liver failure, and recurrent sepsis due to biliary obstruction are among the main causes of mortality. Although the 1-year survival has increased over time, from 16% in 1975–1979 to 28% in 1995–1999, the 5-year survival, by contrast, has not shown any significant change [11]. Globally, hepatobiliary malignancies account for 13% of cancer-related deaths; 10–20% of these are attributable to CCA [1].

4. Classification

CCA may arise from biliary epithelium in each portion of the biliary system. According to the staging of the American Joint Committee on Cancer (AJCC) [12] and the Union for International Cancer Control (UICC) system [13], CCA is classified according to its anatomical location as intrahepatic (iCCA), perihilar (pCCA), and distal CCA (dCCA). In a large series of patients with bile duct cancer, 8% had iCCA, 50% had pCCA, and 42% had dCCA [14].

Based on the classification of the Liver Cancer Study Group of Japan, iCCA can be classified by macroscopic growth patterns as mass-forming (MF-iCCA), periductal infiltrating (PI-iCCA), and intraductal growing iCCA (IG-iCCA) [2]. iCCAs are highly heterogeneous tumors and several classifications have been proposed [15–18]. Two types of candidate stem/progenitor cells of the biliary tree are considered to exist at the peribiliary glands for large bile ducts and at the canals of Hering for small ducts [19, 20]. Mucin-producing cells of segmental biliary ducts may give rise to tubular adenocarcinoma producing mucin with or without micropapillary structures [21]. Instead, iCCA originating from the ductular epithelium may exhibit mixed characteristics between hepatocellular and cholangiocellular carcinoma. In fact, bile ducts are composed of progenitor liver cells capable of differentiating both hepatocytes and cholangiocytes [22]. The mixed iCCA type (bile ductular) is frequently associated with chronic liver diseases (viral hepatitis or cirrhosis). The mucinous iCCA (bile duct) is more frequently associated with primary sclerosing cholangitis (PSC) [23]. The mass-forming type iCCA is characterized by a well-defined and lobulated mass with a various degree of sclerotic change of the tumor center in the liver parenchyma. When iCCA arises in a cirrhotic liver or is small sized, it exhibits an ill-defined tumor border. Necrotic or hemorrhagic changes can be recognized in larger MF-iCCA. The longitudinal extension along the large bile ducts is peculiar of the periductal infiltrating type. Dilation of the peripheral bile ducts and cholestasis are evident when biliary stenotic changes occur. The proliferation within the lumen of large bile ducts is characteristic of the intraductal growth type. This type shares the features of intraductal papillary neoplasms of the bile duct [16].

5. Risk factors

5.1. Primitive sclerosing cholangitis

Primitive sclerosing cholangitis (PSC) is the best-known predisposing condition in Western countries. The cumulative annual risk is 1.5% after the onset of jaundice and the prevalence of cholangiocarcinoma is between 8 and 40% [3]. A Dutch epidemiological study showed that the risk of CCA in patients with PSC was 9% at 10 years from diagnosis, and patients with a concomitant inflammatory bowel disease (IBD) presented a risk at 10 and 20 years, respectively, of 14 and 31%, significantly higher than patients without IBD, 2% at 10 and 20 years ($p = 0.008$) [24]. Predictive prognostic factors of CCA onset are sudden and progressive

jaundice, unintended weight loss, biliary dilatation proximal to the stenosis, CA 19-9 increase over 100 U/mL, and cell dysplasia on bile duct cytological brushing [24].

5.2. Parasitic infections

Numerous experimental and epidemiological data suggest the association between hepatic parasitic infestation by *Opisthorchis viverrini* or *Clonorchis sinensis*, the so-called oriental cholangiopathies and the CCA [3], whose eggs released in the guest biliary system accumulate progressively causing chronic inflammation and therefore increasing the risk of CCA development [11].

5.3. Fibropolycystic liver disease

Congenital malformations of the biliary tree associated with Caroli disease, congenital hepatic fibrosis and coledochal cysts are responsible for 15% risk of developing a cholangiocarcinoma after the second decade, at an average age of 34 years. The overall incidence of this neoplasia in patients with untreated cysts is 28% [25]. Bile duct adenomatosis and biliary papillomatosis are also associated with the development of CCA [3].

5.4. Intrahepatic biliary stones

Hepatolithiasis is rare in Western countries but relatively common in some regions of Asia, and in 10% of the affected patients, it is responsible for the development of iCCA [26].

5.5. Exposure to chemical carcinogens

Numerous chemical compounds have been suspected to induce CCA. Thorotrast, a radioactive contrast medium based on Torus dioxide, requires a special mention. Broadly used in radiology between 1920 and 1950, it has been shown to be responsible for increasing the risk of CCA by 300 times in the general population [27, 28]. Several minor studies have identified other carcinogenic chemicals such as asbestos, vinyl chloride, nitrosamines, isoniazid, and first-generation oral contraceptives [29].

5.6. Viral hepatitis

The risk of developing a CCA on a cirrhotic liver is 10 times greater than the general population: 0.7 versus 10.7% [30]. A Korean case-control study showed that 12.5% of CCA patients were positive for C virus (HCV) and 13.8% were positive for the surface antigens of hepatitis virus B (HBsAg) compared with 3.5 and 2.3% of controls [31]. In 2000, a prospective Japanese study reported that the risk of developing CCA in HCV patients was 3.5% at 10 years, 1000 times greater than the risk of the general population [32]. A large US epidemiological study has shown that HCV infection is a risk factor for iCCA (hazard ratio: 2.55; IC 95%: 1.3–4.9) but not for the extrahepatic variant (hazard ratio: 1.5; IC 95%: 0.6–1.85) [33]. Although the human immunodeficiency virus (HIV) does not cause cirrhosis by itself, 0.5% of infected patients developed a CCA as compared to 0.1% of controls, confirming previous observations that chronic viral infections can predispose to the neoplastic transformation of some cell lines [34].

6. Prevention and screening

For patients with PSC, brush cytological examination or biopsy may be used as a surveillance tool for the early detection of cellular atypia. In high-risk areas, where liver infection is endemic, prevention of cholangiocarcinoma may be achieved by early treatment of infection.

7. Pathogenesis

Biliary epithelial carcinogenesis is a multistep process that involves the transition from hyperplasia to dysplasia to carcinoma. Chronic inflammation, cell damage, and bile flow obstruction lead to chronic exposure of cholangiocytes to the carcinogenetic action of biliary components. The bile of patients with biliary inflammatory diseases contains increased levels of oxysterols, oxygenated cholesterol derivatives, which can promote carcinogenesis by inducing COX-2 expression, EGF (epidermal growth factor receptor) transactivation, by suppressing E-cadherin, and blocking the degradation of Mcl-1 (myeloid cell leukemia protein 1) [35]. The neoplastic transformation of the biliary epithelium is accompanied by numerous molecular and genetic alterations. Abnormal cell proliferation and survival are induced by the activation of autonomous growth factors such as HGF/Met, IL-6, ErbB2, K-ras, BRAF, and COX-2. Alterations in the DNA repair mechanisms, such as microsatellite instability, increase the risk of genetic damage. Immortalization of biliary cells is mediated by the modulation of telomerase activity and by the inactivation of numerous oncosuppressor genes. For example, inactivating mutations or loss of heterozygosity (LOH) of p53 (occurring from 20 to 70% in CCA cells), hypermethylation of the promoter with the inactivation of p16, and increased cyclin D1 are among the more responsible for the deregulation of the cell cycle. In addition, the hyperexpression of anti-apoptotic proteins, such as Bcl-2, Bcl-xl, and Mcl-1, is responsible for the alteration of programmed death mechanisms. Eventually, invasion and metastases are favored by the loss of E-cadherin and catenins. Angiogenesis is promoted by VEGF, COX-2, and TGFβ1 [35]. Calcium S100A4 binding protein, normally expressed at a cytoplasmic level in the epithelial cells and at a nuclear level in mesenchymal cells, is increased in those cells who underwent neoplastic transformation, thus identifying a CCA subtype that responds significantly less to surgical therapy [36].

8. Tumor stroma and tumoral progression

Carcinogenesis has been recognized as a multi-step process during which cancerous cells accumulate multiple and consecutive genetic alterations. Only in recent years, tumor progression has been recognized as the product of a dynamic crosstalk between the various cells of tumor parenchyma and the surrounding tissue, the tumor stroma [37]. The interaction between parenchymal cells and the stromal microenvironment can largely determine the

tumor phenotype [38]. Invasive carcinomas are often associated with the expansion of the tumoral stroma and increased extracellular matrix deposition [39]. Cancer cells can modify the adjoining stroma to create a permissive and supportive microenvironment that supports tumor growth.

Knowledge and control of the tumor microenvironment is becoming as important as that of cancer cells in understanding biology and in defining new therapeutic approaches [40]. Morphological evidences describe it as a "desmoplastic" reaction that contains many cell types [41]. Endothelial cells, tumor-associated macrophages, and cancer-associated fibroblasts (CAFs) promote tumor growth and progression. CAFs are large elongated mesenchymal cells whose characteristic immunohistochemical markers are Alpha Smooth Muscle Actin (α-SMA), Fibroblast Activation Protein (FAP), Thy-1, Desmin, and Protein S100A4 [42, 43]. CAFs can derive from quiescent fibroblasts, epithelial cells through epithelial-mesenchymal transition (EMT), medullary mesenchymal cells, or endothelial cells [44]. In the scenario of tumor growth, CAF secretes and synthesizes type I and IV collagen, fibronectin, proteoglycan, heparan sulfate, connective tissue growth factor, and plasminogen activator. Moreover, CAFs are an important source of proteases that degrade the extracellular matrix (ECM) as MMPs (metalloproteinases) that play an important role in tumorigenesis [45]. Recruitment and accumulation of CAFs in tumor stroma allow these cells to actively communicate with inflammatory, tumor, epithelial, endothelial, and peripheral cells through the secretion of numerous growth factors, cytokines, and chemokines (TGFβ, PDGF, and HGF) that play a role in the initiation of tumor progression [46–49]. The stroma of cholangiocarcinoma undergoes profound changes in its composition during cholangiocarcinogenesis with an upregulation of genes related to the cell cycle, extracellular matrix, TGFβ pathway, and inflammation [50, 51]. The desmoplastic stroma of intrahepatic cholangiocarcinoma is often rich in positive αSMA fibroblasts surrounding the ducts, glandular structures, and neoplastic cholangiocyte aggregates (**Figure 1**). Patients with iCCA having a desmoplastic reaction rich in positive αSMA-CAF have a significantly lower overall survival and a disease-free survival than iCCAs with αSMA lower levels [52]. For example, a study by Chuaysri et al. reported a significantly higher αSMA expression in tumors larger than 5 cm, and survival analysis in 52 patients with 5-year follow-up shows that 31 patients with higher levels of αSMA present 6% survival than 29% of patients with lower expression levels ($p = 0.013$) [53].

Cell survival and resistance to chemotherapy are mediated by periostin, PDGF-BB, sphingosine-1-phosphate (S1P), and prostaglandin E2 by activating the Akt/PKB pathway. The

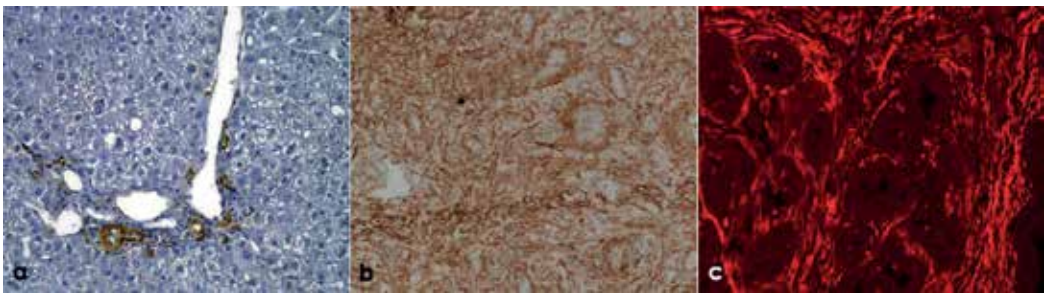

Figure 1. Alpha-SMA expression in normal liver parenchyma (in brown, a) and in cholangiocarcinoma specimen at immunohistochemistry (b) and at immunofluorescence (in red, c), personal series.

action on the extracellular matrix (ECM) of CAFs is mediated by the activation of different metalloproteinases (MMP-1, -2, -9) and secretion of various profibrotic proteins such as TGFβ, PDGF-B, connective tissue growth factor (CTGF), SDF-1, angiotensin II, and IGFBP-5/-7 (insulin growth factor-binding protein-5/-7) [54].

9. Clinical features

Rarely, cholangiocarcinoma occurs in subjects under 40 years of age and the characteristic signs of presentation depend on the location along the biliary tree. The lesions at the biliary bifurcation or at the distal common bile duct present with the sequelae of biliary obstruction: jaundice, clay-colored stools, and dark urine. Peripheral tumors, which originate from the intrahepatic ducts, tend to occur with nonspecific symptoms such as malaise, weight loss, abdominal pain, hepatomegaly, right upper abdominal mass, and fever. Cholangitis is an atypical presentation mode. However, in general, the disease remains silent until an advanced stage. In fact, iCCAs are incidentally diagnosed in up to 12–30% of patients and are asymptomatic in up to 30–73% of all diagnosed cases. This nonspecific and aggressive behaviour leads to the reported unresectability at presentation in half of all patients [55–57].

10. Diagnosis

Diagnostic confirmation can be made difficult by the wide spectrum of alternative diagnoses including benign pathologies (iatrogenic lesions, PSC and choledocholithiasis) and other cancers such as gall bladder cancer and ab extrinseco compression. The clinical approach should be multidisciplinary, and the diagnosis of intrahepatic CCA should be considered when there is an histological finding of adenocarcinoma without any other evidences of an extrahepatic primitive neoplasia.

11. Diagnostic procedures

11.1. Serologic tests

Serologic tests are characterized by the nonspecific elevation of serum bilirubin and liver enzymes, alkaline phosphatase, γ-glutamyltranspeptidase and less commonly transaminases. There are no cancer-specific markers for cholangiocarcinoma. The most commonly used are CA19-9 and CEA, but the optimal cut-off level for suspicion of cholangiocarcinoma is not known [58]. Their diagnostic utility is limited due to their low sensitivity (50–63% and 15–68%, respectively). Ca 19-9 can be significantly elevated in other malignancies and in inflammatory and infectious conditions. Furthermore, up to 10% of the population shows a Lewis-negative blood-group phenotype, thus resulting in an unuseful marker [59]. After curative resection, both serum levels decrease from a preoperative level.

11.2. Radiological techniques

Abdominal ultrasound is the first level survey. It reaches a sensitivity and a specificity of 89 and 95%, respectively, in confirming the dilatation of intrahepatic biliary ducts, locating the site of obstruction, and excluding the presence of lithiasis [4]. The mass-forming subtype usually appears as a homogeneous, hypoechoic lesion, while the periductal infiltrating subtype presents as a small mass-like lesion or as a diffuse biliary tract thickening. However, ultrasound is limited because of nonspecific findings, and therefore, it is not capable of differentiating the nature of the lesion (iCCA, HCC, metastases). If a suspect lesion is detected by ultrasonography, further cross-sectional imaging is required for confirmation [60, 61] (**Figure 2a–c**).

Computed tomography (*CT*) is highly susceptible to determining intrahepatic neoplastic lesions of at least 1 cm in diameter, locating the site of biliary obstruction and the presence of lymphadenopathy [3]. ICCA may present with central diffuse hypoenhancement due to fibrotic

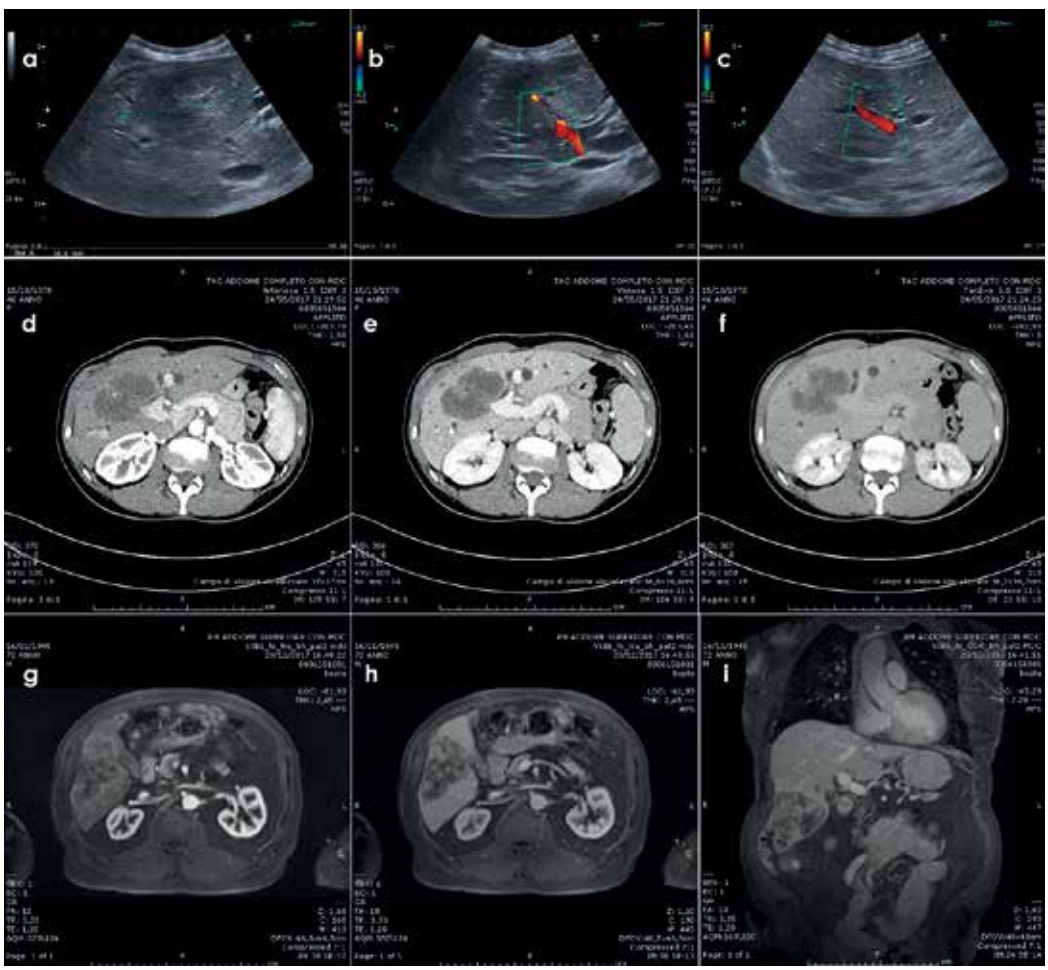

Figure 2. Mass-forming intrahepatic cholangiocarcinoma. (a–c) Abdominal ultrasound confirming the dilatation of intrahepatic biliary ducts, locating the site of obstruction. It appears as a homogeneous, hypoechoic lesion. (d–f) CT scan, the lesion is hypoenhanced, with capsular retraction and biliary dilatation. Right portal vein invasion can be noted. (g–i) MRI is characterized by peripheral enhancement followed by progressive centripetal filling.

remodeling, capsular retraction caused by liver atrophy (21–36% of all cases), dilated bile ducts distal to the mass, or satellite nodules [60] (**Figure 2d–f**).

Magnetic resonance imaging (*MRI*) is the gold standard, with diagnostic potential greater than CT with 88% sensitivity and 95% specificity. In addition to identifying intraepithelial lesions, it allows to create three-dimensional reconstructions of the biliary tree (cholangiopancreatography phases) allowing the evaluation of the upstream and downstream biliary ducts and it determines the extent of biliary invasion, vessel infiltration, local lymphadenopathy, and distant metastases [4]. ICCAs appear hypointense on T1-weighted images and heterogeneously hyperintense on T2-weighted images with a central hypointensity due to fibrotic remodeling and necrosis in mass-forming subtypes. The contrast-enhanced MRI is characterized by peripheral enhancement followed by progressive centripetal filling and contrast pooling on delayed images [62] (**Figure 2g–i**).

Positron emission tomography (*PET*)*-CT* with deoxy-fluoroglucose is able to identify neoplastic lesions of the bile ducts >1 cm in diameter, although it is less useful in evaluating infiltrating masses [4]. Its diagnostic value is controversial. In evaluating MF-iCCAs, it has a sensitivity of about 85–94%, but the sensitivity in other subtypes is poor (18%) [62]. However, some studies revealed that PET-CT was able to detect occult metastases in 20–30% of all patients, which have not been identified by CT or MRI [61].

11.3. Pathological diagnosis

Making a tissue diagnosis of cholangiocarcinoma is not easy because of its location, size, and desmoplastic characteristics. Bile cytology can be obtained with fine needle aspiration with ultrasound or CT guidance; brush cytology can be obtained with ERCP or an endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). Adenocarcinoma is the most common histological findings in iCCA and can be difficult to distinguish from metastatic adenocarcinomas. Immunohistochemical (IHC) evaluation may improve its accuracy. ICCA diagnosis is suggested by TTF1 (lung), CDX2 (colon), and DPC4 (pancreas) negative findings, while AE1/AE3, CK7, and CK20 positive findings suggest the biliary origin of the disease. Liver biopsy in non-cirrhotic patients candidate to a curative resection is not required due to the risk of tumor spread and hemorrhage [59, 62].

11.4. Additional assessment

Depending on the fact that secondary metastasis is more frequent than iCCAs, a careful evaluation is needed to rule out other primary malignancies. This should include: chest X-ray, esophagogastroduodenoscopy (EGDS), and colonoscopy. In women, a gynecologic evaluation and a mammography should be performed.

12. Clinical staging

Currently, there is no consensus regarding a staging system for iCCA [21, 63]. Individual staging systems for iCCA had previously been proposed by the National Cancer Center of Japan (NCCJ) staging system by Okabayashi et al. [64], and Yamasaki proposed a staging system based on the Liver Cancer Study Group of Japan (LCSGJ) [65]. However, these

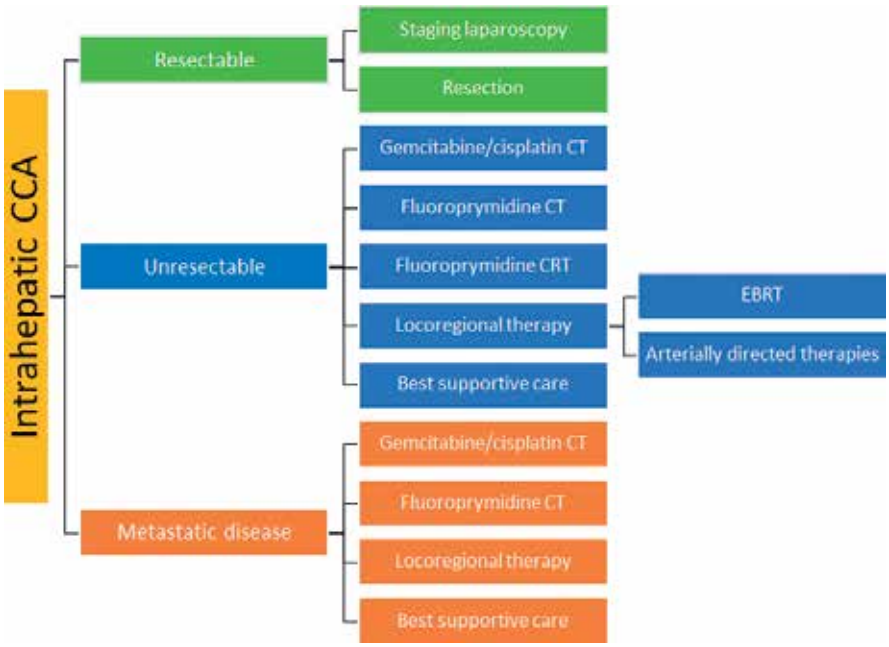

Figure 3. Treatment flowchart.

staging systems were never validated and widely used in the Western countries. Given the lack of a proposed staging system in the West, Nathan et al. [66] analyzed the Surveillance, Epidemiology, and End Results database (SEER database) aimed at developing a staging system for iCCA. In 2010, the seventh edition of AJCC/UICC staging manual adopted most of the recommendations from the staging system proposed by Nathan et al. and published the first unique staging system for ICC. The new classification focuses on multiple tumors, vascular invasion, and lymph node metastasis. The eighth edition has been recently published with several notable changes to the T-category classification schema. The 8th edition introduces T1a and T1b subgroups, which discriminate the T1 group based on the cut-off of 5 cm. Periductal invasion is removed from the T4 category, which is now defined as the direct invasion of local extrahepatic structures, also classified as Stage IIIB (previously Stage III). Nodal staging is defined by the minimum recover y of six lymph nodes. Subsequently, Spolverato et al. [67] published a comparative performance analysis between the 7th and 8th edition demonstrating that the revised edition can better stratify the risk of death of Stage III and T3 patients (**Figure 3**).

13. Surgical management

13.1. Preoperative evalutation

Postresection liver failure (PLF) remains the most important factor associated with postoperative mortality after major liver resections (resection of 4 or more Couinaud liver segments)

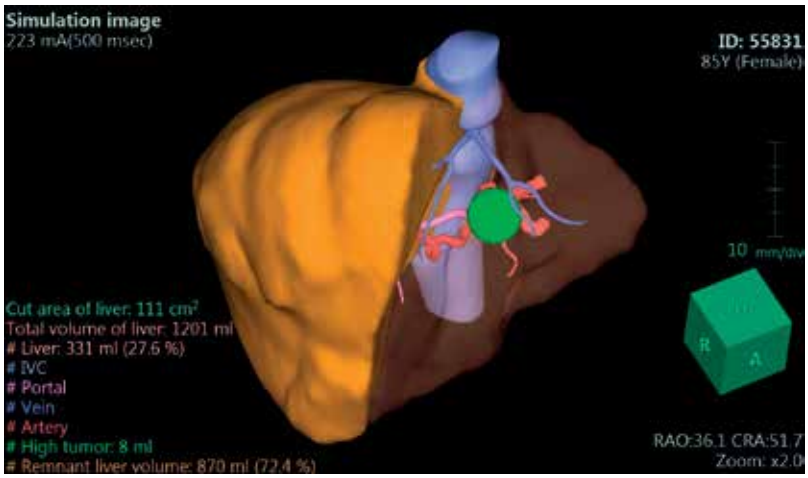

Figure 4. Volumetric liver analysis. It is performed to determine total liver volume (TLV) and future remnant liver volume (FRLV) and remnant liver volume percentage (RLV%).

[68–70]. Prevention of this severe and often lethal complication is attempted through a careful preoperative liver evaluation. In our center, the liver function is determined by the combined analysis of volumetric liver assessment, liver functional MRI, and the indocyanine green clearance retention test.

13.1.1. Volumetric liver analysis

A CT- or MRI-based volumetric liver analysis is performed to determine total liver volume (TLV) and future remnant liver volume (FRLV), and remnant liver volume percentage (RLV%) is then calculated. In patients with healthy livers, approximately 25% of the liver parenchyma needs to be preserved to prevent PLF. In damaged, post-chemotherapy or cirrhotic livers, up to 50% liver parenchyma needs to be spared [71–74] (**Figure 4**).

13.1.2. MRI-based segmental liver function

MRI-based T1 relaxometry with the liver-specific contrast agent gadolinium-ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) is a useful method for assessing overall and segmental liver function [75]. Gd-EOB-DTPA is a hepatocyte-specific MRI contrast agent. Due to its hepatocyte-specific uptake and paramagnetic properties, functioning areas of the liver exhibit shortening of the T1 relaxation time. Reduced liver function correlates with decreased Gd-EOB-DTPA accumulation in the hepatocytes during the hepatobiliary phase.

13.1.3. Indocyanine green clearence test

Indocyanine green retention rate at 15 minutes (ICG-R15) has been widely used as a routine guideline in Eastern countries for making appropriate surgical decisions in hepatocellular carcinoma patients, and recent evidence suggests that ICGR-15 is applicable to Western populations for evaluating preoperative liver function. The ICG clearance test is performed by

administering intravenously a dose of 0.5 mg/kg ICG. The ICG plasma disappearance rate (PDR) is then measured transcutaneously using a near-infrared finger clip sensor. The ICG retention rate at 15 minutes (R15) is then calculated. The ICG retention value at 15 minutes (ICG R15) after injection is approximately 10% in normal persons, and this value is used for stratification of patients [76, 77].

Patients eligible for surgery should have a good performance status. Albumin and bilirubin level are predictors of the risk of PLF. In 1996, Su et al. published the results of a multivariate analysis which disclosed that an adequate nutritional support to increase serum albumin over 3 g/dL is the most important factor to decrease postoperative mortality and that total bilirubin > or = 10 mg/dL is associated with poorer survival [78]. As such, preoperative management should include biliary drainage (endoscopic or percutaneous) and portal vein embolization in patients with obstructive jaundice or with an insufficient remnant liver volume percentage, respectively.

13.2. Surgery

Surgical resection with histologically negative margins is the only curative treatment for iCCA. R0 resection rates can approach 85% with an aggressive surgical approach that often involves a major/extended hepatectomy and vascular and bile duct resection (**Figure 5**). The size, the location of the lesion, and the degree of tumor infiltration determine the extent of resection. The 5-year overall survival (OS) rate is null in patients with positive margins and almost 40% with negative margins. Indeed, aggressive surgical strategies are vital for long-term survival. Unfortunately, only few patients are candidates for surgery, and therefore, the surgeon must be involved from the beginning in the diagnostic path to ensure an early approach [29, 57, 79]. Positive tumor margins, lymph node metastases, cirrhosis, especially advanced cirrhosis with Child-Pugh score beyond A, and presence of portal hypertension are associated with poor outcomes in surgical cohorts [57, 80]. In patients with bilateral, multifocal, or multicentric disease, resection should be avoided. Contemporary studies do not support the option of liver transplantation for intrahepatic cholangiocarcinoma unlike for selected patients with perihilar cholangiocarcinoma [81]. Staging laparoscopy, whose role has not yet been fully elucidated, could be useful in the

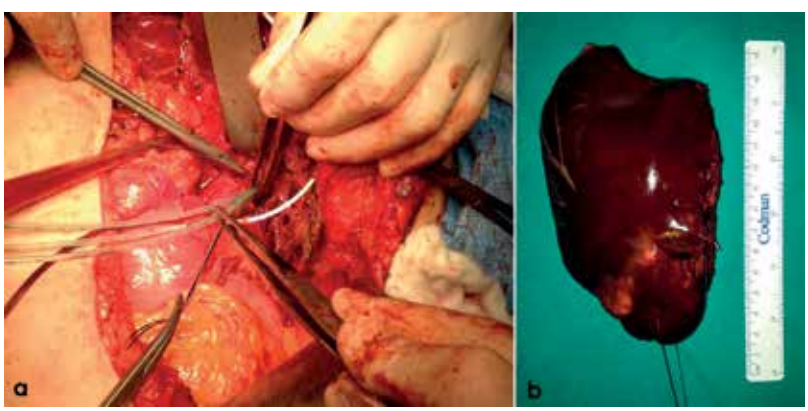

Figure 5. Intrahepatic CCA. (a) Left hepatectomy, biliary resection, and bilioenteric anastomosis with right anterior bile duct S5/8, right posterior bile duct S6/7, and segmental S1 bile duct and (b) left lateral sectionectomy.

assessment of peritoneal implants. The 2015 Consensus on iCCA stated that it should be utilized in high-risk patients (multicentric disease, high CA 19-9, questionable vascular invasion, or suspicion of peritoneal disease) [62]. The 2015 expert consensus on iCCA stated that lymphadenectomy should always be performed as part of the standard surgical treatment due to the high incidence of node metastasis and its prognostic importance. Even though the incidence of nodal metastasis is high, reaching 40% in some studies, data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) registry show that only 55% of patients have pathologic evaluation of at least one regional lymph node [57, 62]. Postoperative complication rate is between 11 and 58%. Bile leakage, postresection liver failure (PLF), abdominal infection, and portal vein embolism are included. Perioperative mortality rate is between 1.2 and 7% [82, 83]. In a recent French study based on 163 patients who underwent potentially curative resection were stratified according to the stage of disease. The 5-year survival was reported to be 32% for all patients; 62% for Stage I (T1 N0); 27% for Stage II (T2 N0), and 14% for Stage III (T3 N0; T1–3, N1). Recurrence may occur in 79% patients at 5 years, despite R0 recurrence. Local recurrence is the most common pattern but is also observed as intrahepatic, nodal, intraperitoneal, or distant metastases [82]. The median survival after recurrence is about 11.1 months in all patients except for those who underwent recurrence resection that is 26.7 months [84]. Mavros et al. in 2014 published in JAMA a systematic review and meta-analysis about the prognosis for patients with iCCA [85]. The meta-analysis was conducted on seven studies (2132 patients), and the shorter overall survival was associated with larger tumor size (hazard ratio 1.09 [1.02–1.16], for each 1 cm increment); multiple tumors (1.70 [1.34–2.02]); lymph node metastasis (2.09 [1.80–2.43]); vascular invasion (1.87 [1.44–2.42]); and poor tumor differentiation (1.41 [1.17–1.71]) [85].

14. Unresectable disease

The majority of patients (89%) die of tumor-related liver failure: biliary obstruction, vascular compromise, or a combination of both. Only 40% of patients will undergo cancer-directed surgery. So, a large proportion of patients could be suitable for liver-directed therapies, even after adjuvant chemotherapy. These options include transarterial chemoembolization (TACE), radioembolization (TARE), hepatic arterial infusion (HAI), percutaneous ablation, and external beam radiation therapy (EBRT) [86]. Which one of these is the best in a given scenario is yet to demonstrate because of the retrospective setting of all the studies published to date.

14.1. Transarterial chemoembolization (TACE)

Retrospective studies of TACE have reported a range of survival times for limited numbers of patients with a variety of chemotherapeutics administered. Cisplatin, doxorubicin microsphere, and mitomycin C alone or in combination have guaranteed an overall survival of 12.3 months [87]; 13 months [88]; 21.1 months [89]; and 30, 13, or 15 months, respectively [90–92].

14.2. Transarterial radioembolization (TARE)

TARE with yttrium-90 (^{90}Y) microspheres has received the most attention by the scientific community. In 2015, Al-Adra et al. systematically reviewed the existing literature regarding

the treatment of unresectable iCCAs. Twelve studies, published between 2011 and 2013, with relevant data regarding TARE were analyzed. The overall weighted median survival was 15.5 months (range: 7–22.2), and the response evaluation criteria at 3 months demonstrated a partial response in 28% and stable disease in 54% patients. What the most, seven patients were able to be downstaged to undergo surgical resection [93].

14.3. Percutaneous ablation

Percutaneous ablation by radiofrequency or microwave is generally indicated for patients with tumors less than 4–5 cm that are not near a segmental bile duct, liver surface, or major vessel. Han et al. in 2015 published a systematic review and meta-analysis about the use of radiofrequency ablation. Seven observational studies, comprising 84 patients, were reviewed. The pooled 1-year, 3-year, and 5-year survival rates were 82% (95% confidence interval [CI], 72–90%), 47% (95% CI, 28–65%), and 24% (95% CI, 11–40%) [94]. Yu et al. in 2011 retrospectively evaluated the experience in treating iCCA with microwave ablation. About 15 patients with a mean tumor size of 3.2 ± 1.9 cm (range, 1.3–9.9 cm) were treated. The cumulative overall 6-, 12-, and 24-month survival rates were 78.8, 60.0, and 60.0%, respectively [95]. Treatment failure, liver abscess, sepsis, and needle seeding are the major complications described with both techniques.

14.4. External beam radiation therapy (EBRT)

High-dose, conformal external beam radiation therapy (EBRT) has emerged as an acceptable treatment for selected patients with localized, unresectable iCCA. Precise determination of cancer location and extent of radiotherapy targeting has been made possible by the contemporary evolution of diagnostic radiology techniques. Advanced EBRT techniques (3D conformal radiotherapy and intensity-modulated radiotherapy) are used to deliver conformal radiation to the target while sparing nonmalignant tissues. Consequently, unresectable iCCA patients can undergo accelerated and hypofractioned regimens to deliver high-dose, ablative EBRT [96–98]. Tao et al. published a single-institution retrospective analysis involving 79 patients with localized, unresectable iCCA treated with high-dose, conformal EBRT (35–100 Gy, median 58.05 Gy, in 3–30 fractions). The median overall survival was 30 months [97]. Hong et al. involved 37 patients with localized, unresectable iCCA in a multi-institutional single-arm phase II study. They received hypofractionated proton beam therapy with a median dose of 58.05 Gy in 15 fractions delivered daily over 3 weeks. The median and 2-year overall survival were 22.5 months and 46.5%, respectively; the 2-year local control rate was 94%, and most recurrences occurred at extrahepatic sites [98]. These outcomes formed the basis for an ongoing randomized phase III trial study to assess how well gemcitabine hydrochloride and cisplatin with or without radiation therapy work in treating patients with localized unresectable iCCA (NCT02200042).

14.5. Hepatic arterial infusion (HAI) chemotherapy

HAI has been developed in colorectal liver metastases, but in the last few years more data are available for iCCA. The Memorial Sloan-Kettering Cancer Center of New York research group led by Kemeny and Jarnagin investigated the efficacy of HAI with floxuridine and dexamethasone in patients with unresectable iCCA or hepatocellular carcinoma (HCC). Thirty-four unresectable patients (26 iCCA and 8 HCC) were treated. Partial responses were seen in 16

patients (47.1%); the median survival was 29.5 months and the 2-year survival was 67% [99]. In 2011, they published the results of a trial in which twenty-two patients (18 iCCA and 4 HCC) were treated by systemic (IV) bevacizumab in addition to the previously described HAI. Median survival was 31.1 months (CI 14.14–33.59) and progression-free survival (PFS) was 8.45 months (CI 5.53–11.05). The trial did not prove the improvement in outcome and was prematurely terminated due to increased biliary toxicity [100].

Our study group recently published the personal experience with this treatment modality. Between 2008 and 2012, eleven patients suffering from an unresectable iCCA underwent HAI chemotherapy with fluorouracil and oxaliplatin. A CT scan performed after the sixth cycle of therapy revealed that 5 of them had partial hepatic response (more than 45%), 2 had stable disease, and 4 showed clear signs of disease progression. The average survival of the entire group was 17.6 months. Three of the patients with partial hepatic response underwent resection and 2 had more than 70% tumor necrosis. The median survival of patients with liver-only disease treated with systemic chemotherapy, who were not submitted for resection, was 15.3 months [101].

Eventually, future randomized trials comparing systemic chemotherapy and liver directed therapies will be required to identify the optimal treatment modality for unresectable iCCA.

15. Chemotherapy

There is still no definitive consensus regarding the standard chemotherapy regimen to treat patients with locally advanced and metastatic iCCA [102]. Treatment recommendations are based on few phase III trial data conducted on heterogeneous patient populations, including patients with gallbladder cancer; intrahepatic, hilar, or distal cholangiocarcinoma; and in some cases ampullary cancer. Furthermore, surgery for iCCA has a relevant morbidity rate (8–10%), which often contraindicate any adjuvant treatment [103].

The role of adjuvant chemotherapy in resected iCCA is still debated and matter of concern because of the recurrence rate in the liver in 50–60% of patients, in the peritoneum in about 20%, and in the portal lymph nodes in 20–30% [62]. Currently, few randomized trials and clinical results are available. A recent meta-analysis by Horgan et al. failed to demonstrate a significant beneficial trend for any adjuvant therapy over observation (HR 0.75, 95% CI 0.55–1.01; P = 0.06). Those receiving chemotherapy or chemoradiotherapy derived statistically greater benefit than radiotherapy alone (OR, 0.39, 0.61, and 0.98, respectively; P = 0.02). The analysis, what the most, supported the adjuvant role of chemotherapy or chemoradiotherapy in those with lymph node positive disease (OR, 0.49; P = 0.004) and R1 disease (OR, 0.36; P = 0.002) [104]. Several ongoing trials will clarify the role of adjuvant chemotherapy: the BILCAP study (capecitabine vs. observation—NCT00363584), the UNICANCER trial (gemcitabine/oxaliplatin vs. observation—NCT01313377), and the Japanese study BCAP (gemcitabine vs. observation—NCT000000820). Until then, there are no definitive data to provide recommendations regarding the optimal adjuvant therapy, but it should be discussed in patients with high risk of recurrence: R1 and N1 stage [62, 103].

For patients with advanced stage cholangiocarcinoma not amenable to locoregional and surgical options, the combination of gemcitabine and cisplatin is the current first-line chemotherapy. In 2010, Valle et al. finally defined the standard treatment for advanced

cholangiocarcinoma in a phase III trial (ABC-02). This study provided concrete support for gemcitabine and cisplatin, demonstrating improvements for the combination compared with gemcitabine alone both in overall survival (11.7 vs. 8.1 months; $P < 0.001$) and in progression-free survival (8.0 vs. 5.0 months; $P < 0.001$) [105].

Other drug combinations have been considered in first-line treatment of advanced disease: capecitabine/oxaliplatin, capecitabine/cisplatin, gemcitabine/capecitabine, or triplets comprehending fluoropyrimidine/gemcitabine/platinum compound. Also, targeted therapies have been investigated: cetuximab, panitumumab, and erlotinib. Overall, there are no sufficient evidences to support new combination therapies as first-line treatment, and no activity has been described for novel targeted therapies [106–114].

16. Palliation

Palliative treatment plays an important role since most CCA patients are not susceptible to resection and the remaining subjects undergoing surgery exhibit a high rate of recurrence. It tends to relieve symptoms, treat sepsis, and normalize bilirubin levels before chemotherapy or radiotherapy treatment. Endoscopic approach is preferable (ERCP) with plastic or metal stent positioning. In case of tumor localization and growth preventing ERCP, percutaneous approach for biliary drainage is safe and equally effective as ERCP.

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Chapter 3

Chemotherapy of Cholangiocarcinoma: Current Management and Future Directions

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Additional information is available at the end of the chapter

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Abstract

Cholangiocarcinoma is a relatively rare form of gastroenterological cancer that divided into intrahepatic, perihilar, and distal bile duct cancer. Approximately, 10,000 new cases are diagnosed annually in the United States, and a 5-year survival rate is below 20%. While only surgical resection can provide a cure, most of cholangiocarcinomas are detected at inoperable stage and associated with poor prognosis. Moreover, cholangiocarcinoma has a high recurrence rate, even after curative surgery. Therefore, chemotherapy has an important role in the treatment of patients with cholangiocarcinoma. International efforts by physicians and researchers are revealing genetic factors of cholangiocarcinoma progression, which will identify early diagnostic markers and novel therapeutic targets. In this chapter, current strategies of adjuvant, neoadjuvant, and palliative chemotherapy will be discussed, as well as expectant future therapeutic targets and development of individualized therapies.

Keywords: cholangiocarcinoma, biliary tract cancer, biliary tract neoplasms, chemotherapy, precision medicine

1. Introduction

Cholangiocarcinoma is a rare malignant tumor that originates from the epithelial cells of the bile duct system. About 90% of cholangiocarcinoma are adenocarcinoma and divided into three forms based on histologic growth pattern as mass-forming, periductal-infiltrating, and intraductal-growing [1]. Generally, cholangiocarcinoma can be divided by anatomical location of biliary tree, as intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma including perihilar cholangiocarcinoma and distal bile duct cancer. Extrahepatic

cholangiocarcinoma is a more common form of cholangiocarcinoma, comprising approximately 80–90% of cholangiocarcinoma. Extrahepatic cholangiocarcinoma consists of perihilar cholangiocarcinoma and distal bile duct cancer. Perihilar cholangiocarcinoma, also called Klatskin tumor, is the most common type, accounting for approximately 50–60% of all cases, and can be defined as a tumor located above the junction of the cystic duct up to and including the second-order biliary branches of the right and left bile ducts [2]. Distal cholangiocarcinoma arose from distal biliary tract above the ampulla of Vater, accounting or approximately 20–30% of all cholangiocarcinoma. Intrahepatic cholangiocarcinoma is in liver parenchyma, accounting for 10–20% of cholangiocarcinoma.

Approximately 10,000 new cases are diagnosed annually in the United States, and 5-year survival rate is below 20% [3]. In Korea, there are 11.2 new cases per 100,000 people annually, and a 5-year survival rate is 29.2% according to cancer statics in 2014 [4]. While only surgical resection can provide a cure, most of cholangiocarcinomas are detected at inoperable stage and associated with poor prognosis. Moreover, cholangiocarcinoma has high recurrence rate, even after curative surgery [5]. Therefore, chemotherapy has an important role in the treatment of patients with cholangiocarcinoma. However, there are only few therapeutic options that establish an effective chemotherapy for advanced cholangiocarcinoma. International efforts by physicians and researchers are revealing genetic factors of cholangiocarcinoma progression, which will identify early diagnostic markers and novel therapeutic targets.

In this chapter, current strategies of adjuvant, neoadjuvant, and palliative chemotherapy will be discussed as well as expectant future therapeutic targets and development of individualized therapies.

2. Adjuvant chemotherapy

2.1. Necessity of adjuvant chemotherapy

Necessity of adjuvant chemotherapy for cholangiocarcinoma is based on prognosis after surgical treatments. Surgery is only curative therapy of cholangiocarcinoma; however, a 2-year survival of cholangiocarcinoma after curative aim surgery was reported very poor. According to a prospective study of 225 patients with hilar cholangiocarcinoma, 80 patients underwent resection, and 48.8% died of disease by 28 months [6]. In this situation, selection of high-risk patients for recurrence after surgery became important. Due to anatomical heterogeneity of cholangiocarcinoma and proximity to other organs, many of previous studies were including cancers originated from the gallbladder or ampulla of Vater as well as intrahepatic and extrahepatic cholangiocarcinoma. Long-term outcomes of curative surgery of cholangiocarcinoma are various according to postoperative stage including nodal status, anatomical location, and histologic margin status. Despite of native difficulties of research about cholangiocarcinoma, the most important conditions proven by previous studies are nodal involvements and histologic margin status after surgery.

A couple of retrospective studies reported postoperative nodal status that is a significant prognostic factor after surgery of extrahepatic cholangiocarcinoma. About 104 patients with distal

bile duct tumors were identified by prospective database. By univariate and multivariate analysis, resectability and negative node status ($P < 0.001$) were the only predictors of favorable outcome [7]. A retrospective single-center experience details of 151 patients after surgical resection of central bile duct carcinoma reported only lymph node metastases, and residual tumor stage proved to be of independent prognostic significance in a multivariate Cox analysis [8]. Another retrospective study of 46 patients who had resection of hilar cholangiocarcinoma by major hepatectomy, bile duct resection, and regional lymphadenectomy reported R0 resection and lymph node metastasis were associated with survival [9]. According to a retrospective study of 320 patients with perihilar cholangiocarcinoma who underwent resection, upon multivariate analysis of the 146 patients with lymph node metastasis, the number of involved nodes (single versus multiple) was identified as an independent prognostic factor (RR of 1.61, $P = 0.045$) [10].

There were studies reported that nodal status was also important in intrahepatic cholangiocarcinoma. About 93 patients who underwent laparotomy for ICC were identified retrospectively, and 46 who underwent curative resection and systematic lymphadenectomy. An increased ratio of positive to total harvested lymph nodes was prognostic for adverse outcome in lymph node-positive patients [11]. In a total of 60 liver resections for mass-forming-type intrahepatic cholangiocarcinoma, the lymphatic invasion index and histological grade were statistically independent prognostic factors for overall survival and recurrence-free survival in multivariate analysis [12].

Resection margin status was also reported as strong independent prognostic factor after surgery in cholangiocarcinoma. In a retrospective analysis of 84 patients with extrahepatic cholangiocarcinoma who underwent surgical resection, ductal resection margin status was classified as negative (n = 64 patients), positive with carcinoma in situ (n = 11 patients), or positive with invasive carcinoma (n = 9 patients). The ductal margin status was found to be a strong independent prognostic factor by both univariate ($P = 0.0002$) and multivariate ($P = 0.0039$) analyses [13]. In 109 patients with resected perihilar tumors, the 1-, 3-, and 5-year survival was 68, 30 and 11%, respectively. The median survival was 19 months. The addition of hepatic lobectomy did not alter the survival rate. Negative margins and negative lymph node status were associated with improved survival [14]. In a prospective study of 225 patients with hilar cholangiocarcinoma, 80 patients underwent resection, and 62 patients showed R0 resection. In the 219 patients whose disease could be staged, the proposed system predicted resectability and the likelihood of an R0 resection and correlated with metastatic disease and survival [6]. In a prospective study of 27 patients with cholangiocarcinoma at the confluence of the hepatic ducts who underwent resection, the difference in survival times between patients with histologic clearance and those with microscopically positive or close (less than 1 mm) resection margins was significant statistically ($P = 0.037$) [15].

In addition, lymphovascular and perineural invasion and large tumor size have been reported as independent predictors of recurrence and reduced overall survival after surgical resection of intrahepatic cholangiocarcinoma [16, 17]. It might be confusing to analyze the studies of bile duct cancers that originate in various locations. However, plenty of studies above reported that marginal resection and lymph node involvement status are significantly associated with surgical outcomes and patient survival. To improve survival of patients after surgical resection, studies of adjuvant chemotherapy were performed.

2.2. Indication and efficacy of adjuvant chemotherapy

Cholangiocarcinoma has various subtypes according to anatomical location, and most of the studies about adjuvant chemotherapy contain patients with gallbladder cancer, ampulla of Vater cancer, or pancreatic cancer. In addition to heterogeneity of the origin of cancers, regimen of chemotherapies and disease status such as post-op stage including lymph node involvement or margin status are also various. Majority of previous studies were retrospective design, except one phase III trial that had not shown a significant outcome improvement after adjuvant chemotherapy.

Several studies were performed to evaluated efficacy of adjuvant chemotherapy for cholangiocarcinoma, and the results were controversial. A retrospective study reported that the benefit of adjuvant chemotherapy after surgery in cholangiocarcinoma is questionable. According to the study including gallbladder cancer and cholangiocarcinoma, of the 157 patients, 17.8% received neoadjuvant chemotherapy, and 48.7% received adjuvant chemotherapy, while 15.8% received adjuvant chemoradiotherapy. Patients with negative margins of at least 1 cm had a 5-year survival rate of 52.4% ($P < 0.01$). Adjuvant therapy did not significantly prolong survival in 94 patients with cholangiocarcinoma [18]. There were other studies that provide positive evidence of adjuvant chemotherapy of cholangiocarcinoma. A retrospective review of 115 patients with hilar cholangiocarcinoma and patients treated with chemotherapy postoperatively had a survival of 43.15 ± 21.02 months, which was significantly longer than the survival of patients who received no postoperatively chemotherapy (36.97 ± 15.99 months; $P < 0.05$) [19].

A systematic review and meta-analysis about adjuvant chemotherapy of cholangiocarcinoma and gallbladder cancer supported adjuvant chemotherapy for biliary tract cancer. About 20 studies involving 6712 patients were analyzed in the study. Among the 20 studies, there were 1 randomized trial of chemotherapy alone, 2 registry analyses, and 17 institutional series. In the overall population, pooled data showed a nonsignificant improvement in survival with any adjuvant therapy compared with surgery alone (OR, 0.74; $P = 0.06$, and for bile duct cancers OR, 0.71; $P = 0.10$). However, after the two registry analyses were excluded, receiving chemotherapy demonstrated statistically greater benefit than surgery alone (P = 0.02). In subgroup analysis, the greatest benefit for adjuvant therapy was in those with lymph node-positive disease (OR, 0.49; $P = 0.004$) and R1 disease (OR, 0.36; $P = 0.002$) [20].

About the chemotherapy regimen, there is only one phase III randomized controlled studies that had proven limited survival benefit. A phase III randomized trial of adjuvant chemotherapy of cholangiocarcinoma, the European Study Group for Pancreatic Cancer (ESPAC)-3 periampullary trial, was performed in 100 centers in Europe, Australia, Japan, and Canada. Of the 428 patients included in the primary analysis, 297 had ampullary, 96 had bile duct, and 35 had other cancers. About 144 patients were assigned to the observation group, 143 patients received fluorouracil chemotherapy, and the other 141 patients received gemcitabine chemotherapy. Median survival for the observation group was 35.2 months, for patients treated with fluorouracil plus folinic acid 38.9 months, and for patients treated with gemcitabine 45.7 months. The hazard ratio (HR) for fluorouracil plus folinic acid versus observation was 0.95 ($P = 0.74$), and for gemcitabine versus observation, 0.77 ($P = 0.10$), not significant by log-rank analysis across the three groups ($P = 0.23$). In secondary analyses adjusting for prognostic variables

using multiple regression analysis, the HR for chemotherapy compared with observation was 0.75 (P = 0.03) and for gemcitabine 0.70 (P = 0.03). Conclusively, adjuvant chemotherapy was not associated with a significant survival benefit in the primary analysis compared with observation; however, multivariate analysis adjusting compounding factors showed survival benefits associated with adjuvant chemotherapy, especially with gemcitabine [21].

According to the results of the meta-analysis and ESPAC-3 trail, adjuvant chemotherapy is effective in patients with cholangiocarcinoma after curative surgery, especially with lymph node-positive and resection margin-positive disease.

2.3. Guideline recommendation for adjuvant chemotherapy

There were two guidelines about adjuvant chemotherapy of cholangiocarcinoma by expert groups.

The National Comprehensive Cancer Network (NCCN) suggests adjuvant chemotherapy after curative surgery of cholangiocarcinoma and regimens according to lymph node and margin status [22]. Although there are limited clinical trial data to establish a standard chemotherapy regimen for intrahepatic cholangiocarcinoma after surgery, recommended regimens based on fluoropyrimidine or gemcitabine chemotherapy. In patients with no residual local disease (R0) resection, observation or clinical trial can be a choice with fluoropyrimidine-based or gemcitabine-based chemotherapy. If the patients have a disease with microscopic margin positive (R1) or positive regional lymph nodes, chemotherapy is recommended than observation. In addition to fluoropyrimidine-based or gemcitabine-based chemotherapy, clinical trial or fluoropyrimidine chemoradiation can be a treatment option. In spite of receiving curative surgery, patients may have residual local disease. In this situation, clinical trial, locoregional therapy such as transarterial chemoembolization, or best supportive care is included as options with chemotherapy with gemcitabine or fluoropyrimidine. NCCN guideline for adjuvant chemotherapy of extrahepatic cholangiocarcinoma is also based on fluoropyrimidine-based or gemcitabine-based chemotherapy. However, there are limited clinical trial data to set a standard therapy. If available, enrollment in a clinical trial is encouraged. If the disease had negative margin or carcinoma in situ at margin without regional nodes, observation, fluoropyrimidine chemoradiation, fluoropyrimidine−/gemcitabine-based chemotherapy, or clinical trial is recommended as treatment options. If patients had positive margin (R1 or R2) or positive regional nodes, fluoropyrimidine chemoradiation followed by additional fluoropyrimidine-based or gemcitabine-based chemotherapy can be considered, as well as fluoropyrimidine−/gemcitabine-based chemotherapy or clinical trial.

The European Society of Medical Oncology (ESMO) clinical practice guidelines for biliary cancer suggest adjuvant chemotherapy for intrahepatic and extrahepatic cholangiocarcinoma after curative aim surgery [23]. ESMO recommendations offer adjuvant therapy to patients on the understanding that the evidence base is weak and encourage enrollment in clinical trials. When the results from previous meta-analysis were employed, chemoradiation is recommended with 45 Gy dose of radiotherapy in fractions of 1.8 or 2 Gy with concurrent 5-fluorouracil or capecitabine [IV, C].

3. Neoadjuvant chemotherapy

There are not enough evidences about neoadjuvant chemotherapy of cholangiocarcinoma. In a retrospective study including gallbladder cancer and cholangiocarcinoma, neoadjuvant therapy delayed surgical resection on average for 6.8 months ($p < 0.0001$). Immediate resection increased median survival from 42.3 to 53.5 months ($p = 0.01$) [18]. A couple of reports addressed possibility to use neoadjuvant chemoradiation before liver transplantation in patients with cholangiocarcinoma [24–28]. In a study of 287 patients with perihilar cholangiocarcinoma using neoadjuvant therapy, 71 patients dropped out before liver transplantation (rate, 11.5% in 3 months). Intent-to-treat survival rates were 68 and 53%, 2 and 5 years after therapy, respectively; posttransplant recurrence-free survival rates were 78 and 65%, respectively [25]. In a retrospective study of patients with hilar cholangiocarcinoma, 71 patients entered in the protocol combining neoadjuvant radiotherapy, chemosensitization, and orthotopic liver transplantation. About 38 patients underwent liver transplantation, and 26 (48%) underwent resection One-, 3-, and 5-year patient survivals were 92, 82, and 82% after transplantation and 82, 48, and 21% after resection ($P = 0.022$) [27]. Of the 57 patients with intrahepatic and hilar cholangiocarcinoma, neoadjuvant and adjuvant therapies resulted in better patient survival after liver transplantation compared with no therapy or adjuvant therapy only (47% versus 20% versus 33%, respectively; $P = 0.03$) [28]. Despite the lack of result from randomized controlled trial, neoadjuvant chemoradiation might be one of treatment options in selected patients with hilar cholangiocarcinoma before liver transplantation. Further prospective trials are needed in large population for establish neoadjuvant therapy as a reliable therapeutic option in cholangiocarcinoma.

4. Palliative chemotherapy

Palliative chemotherapy has an important role in the treatment of advanced and recurrent cholangiocarcinoma. The current standard therapy for patients with inoperable cholangiocarcinoma is a combination of gemcitabine and cisplatin chemotherapy. A previous randomized controlled trial revealed that combining gemcitabine with cisplatin improved the overall survival by 3.6 months compared to gemcitabine alone [29]. According to the study, gemcitabine with cisplatin combination became the standard therapy of advanced and metastatic cholangiocarcinoma. However, there is no established second-line palliative chemotherapy that could be used after failure of gemcitabine-based chemotherapy. Moreover, cisplatin is associated with severe toxicity, including dose-dependent nephrotoxicity and neurotoxicity, which may limit the opportunities for second-line treatment after disease progression.

4.1. First-line chemotherapy

Benefits of chemotherapy for advanced biliary tract cancer were reported by various studies. In a phase III trial of patients with 53 pancreatic cancer and 37 biliary tract cancer, patients were randomized to a chemotherapy group in addition to the best supportive care or to the

best supportive care group. Chemotherapy was either sequential 5-fluorouracil/leucovorin combined with etoposide or in elderly and poor performance patients, the same regimen without etoposide. Overall survival was significantly longer in the chemotherapy group (median 6 versus 2.5 months, $P < 0.01$) [30]. A pooled analysis of clinical trials reported analysis of the effect of chemotherapy in advanced biliary tract cancer. The study included 104 trials with 2810 patients, thereof 634 responders and 1368 patients with tumor control. Superior response rates and tumor control rates of gemcitabine and platinum-containing regimens were found in the results [31]. A multicenter retrospective study showed that patients receiving gemcitabine had a benefit in survival compared to cisplatin-based regimen or fluoropyrimidine-based regimen or the best supportive care in 304 patients with advanced biliary tract cancer [32]. Upon a base of the results of the previous studies about the efficacy of the first-line chemotherapy for advanced cholangiocarcinoma, a lot of phase II studies were tried to evaluate therapeutic efficacy of combination chemotherapy in advanced cholangiocarcinoma.

4.1.1. Fluoropyrimidine-based combination therapies

Several studies evaluated fluoropyrimidine-based combination therapies. A randomized phase II trial of weekly high-dose 5-fluorouracil with and without folinic acid and cisplatin in patients with 58 advanced biliary tract carcinoma reported similar response rate, progression-free survival, and overall survival [33]. Another phase II trial in 42 patients with advanced biliary tract carcinoma reported 5-fluorourasil continuous infusion, and low-dose consecutive cisplatin therapy appeared to be a useful modality with over all response rates (42.9%) and median survival time (225 days) [34].

4.1.2. Gemcitabine-based combination therapies

A couple of gemcitabine-based combination therapies were tried in advanced cholangiocarcinoma. One randomized phase II trial compared mitomycin C in combination with capecitabine or biweekly high-dose gemcitabine in patients with 51 advanced biliary tract cancer. As a result, mitomycin C in combination with capecitabine seems to be superior in terms of response rate (31 versus 20%), progression-free survival (5.3 versus 4.2 months), and overall survival (9.25 versus 6.7 months) [35]. Gemcitabine with oxaliplatin combination therapy was tried in phase II trials [36–38]. These studies demonstrated moderate efficacy and tolerability. In one of the studies of 70 patients with advanced biliary tract cancer, the objective response rate was 20.5% in non-bladder biliary tract cancers [37]. Combination of capecitabine with gemcitabine therapy demonstrated active and well-tolerated performance as first-line chemotherapy for advanced biliary cancer [39–41]. In a phase II trial, a total of 44 patients received a combination of capecitabine with gemcitabine as first-line therapy and reported median time to disease progression of 6 months and overall survival of 14.0 months [39]. In another phase II trial, capecitabine plus cisplatin combination was reported as well-tolerated regimen for advanced biliary cancer [42]. Some of the study groups reported trials of gemcitabine- and 5-fluorouracil-based combination therapy [43, 44]. With 42 advanced biliary tract cancer patients, a combination of gemcitabine, 5-fluorouracil (5-FU), and leucovorin (LV) demonstrated median time to disease progression as 4.6 months and median survival period as 9.7 months [43].

Triplet chemoregimen also has been tried as first-line chemotherapy for advanced diseases [44–46]. A phase III study of 5-FU, etoposide, and leucovorin (FELV) compared to epirubicin, cisplatin, and 5FU (ECF) was tried in patients with advanced biliary tract cancer. The median overall survival for ECF was 9.02 months and FELV 12.03 months ($p = 0.2059$) in 54 patients randomly assigned to each arm. Objective response rates were similar for both arms (ECF 19.2% versus FELV 15%, $p = 0.72$). However, grade 3/4 neutropenia was significantly increased with FELV versus ECF (53.8 versus 29.5%, $P = 0.020$). In conclusion, ECF did not improve OS compared to FELV, but was associated with less acute toxicity [45].

4.1.3. Gemcitabine with cisplatin combination therapy

Among gemcitabine-based chemotherapy combination, there were several studies of gemcitabine plus cisplatin combination. These studies evaluated efficacy and safety of gemcitabine plus cisplatin combination with one-armed phase II trial, and they reported potent efficacy and good tolerability of this combination [47–49]. A randomized phase II trial, the advanced biliary cancer (ABC)-01 trial, had found gemcitabine with cisplatin combination associated with an improved tumor control rate, 6 months of progression-free survival (47.7–57.1%) compared to gemcitabine alone in 86 patients with advanced cholangiocarcinoma [50]. ABC-01 trial was extended to a phase III trial, the ABC-02 trail, and the study results were published in 2010. A total of 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer were randomly assigned to either cisplatin followed by gemcitabine or gemcitabine alone. The median overall survival was 11.7 months in the cisplatin-gemcitabine group and 8.1 months among the gemcitabine group ($P < 0.001$). The median progression survival (8.0 versus 5.0 months, $P < 0.001$) and tumor control rate (81.4 versus 71.8%, $p = 0.049$) were improved in cisplatin-gemcitabine group. Adverse events were similar in the two groups, with the exception of more neutropenia in the cisplatin-gemcitabine group [29]. After ABC-02 trial, another study of 84 patients with advanced cholangiocarcinoma also reported that cisplatin-gemcitabine combination showed better survival rate and survival time compared to gemcitabine alone [51].

According to the results of ABC-02 trial, gemcitabine plus cisplatin combination became the standard treatment option for first-line chemotherapy for advanced and metastatic cholangiocarcinoma.

4.1.4. Target agents

In addition to combination of cytotoxic chemotherapy agents, combination regimen with target agents was studied in several phase II trials.

A couple of studies evaluated a possibility of epidermal growth factor receptor (EGFR) inhibitors as combination agent with conventional chemotherapeutic agents. A phase II trial of gemcitabine, irinotecan, and panitumumab in advanced cholangiocarcinoma demonstrated the median progression-free survival as 9.7 months and the median overall survival as 12.9 months in 35 patients [52]. Another EGFR-targeted monoclonal antibody, cetuximab, was tried in phase II studies. In 30 patients with advanced biliary tract cancer, cetuximab,

gemcitabine, and oxaliplatin combination demonstrated 63% of objective response rate (10% of complete response and 53% of partial response) [53]. Because of the promising results of this study, the addition of cetuximab to gemcitabine and oxaliplatin did not seem to enhance the activity of chemotherapy in patients with advanced biliary cancer in the randomized phase II BINGO study. In the study, 76 patients were assigned to chemotherapy plus cetuximab and 74 to chemotherapy alone. The median progression-free survival was 6.1 versus 5.5 months, and the medial overall survival was 11.0 versus 12.4 months in chemotherapy plus cetuximab and chemotherapy alone group, respectively [54].

Another phase II study tried the application of sorafenib, an oral multi-tyrosine kinase inhibitor, with gemcitabine. Gemcitabine plus sorafenib versus gemcitabine alone was compared in advanced biliary tract cancer, and there was no difference in the median progression-free survival for gemcitabine plus sorafenib versus gemcitabine alone (3.0 versus 4.9 months, $P = 0.859$) and no difference for median overall survival (8.4 versus 11.2 months, $P = 0.775$). In conclusion, the addition of sorafenib to gemcitabine did not demonstrate improved efficacy in advanced biliary tract cancer patients [55].

Cediranib, an oral inhibitor of VEGF receptors 1, 2, and 3, was evaluated in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer by a randomized phase II trial. As a result, cediranib did not improve the progression-free survival of patients with advanced biliary tract cancer in combination with cisplatin and gemcitabine compared to placebo (8.0 versus 7.4 months, $p = 0.72$) [56].

With the results described above, there was not enough evidence to use target agents in advanced cholangiocarcinoma, and further study seems to be needed.

4.2. Second-line chemotherapy

There was not enough evidence about efficacy of second-line chemotherapy for advanced chemotherapy. In a systematic review of second-line chemotherapy in advanced biliary cancer including 25 studies, 14 phase II clinical trials, 9 retrospective analyses, and 2 case reports evaluate the level of evidence for the use of second-line chemotherapy. A total of 761 patients were evaluated, the mean OS was 7.2 months, and the mean progression-free survival, and response and disease control rates were 3.2 months and 7.7 and 49.5%, respectively. In conclusion, there is insufficient evidence to recommend a second-line chemotherapy schedule in advanced biliary tract cancer [57]. Still, the efficacy of second-line chemotherapy for advanced cholangiocarcinoma is not definite. Further prospective randomized trials are needed to develop evidence of second-line chemotherapy for advanced cholangiocarcinoma.

4.3. Guideline recommendation for palliative chemotherapy

The National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) suggest guidelines for chemotherapy in advanced biliary tract cancer.

NCCN guidelines recommend gemcitabine and cisplatin combination therapy as first-line chemotherapy with a category 1 recommendation for patients with advanced biliary tract

cancer [22]. Gemcitabine-based and fluoropyrimidine-based combination chemotherapies are other options with a category 2A recommendation. Based on the results of phase II trials, gemcitabine with oxaliplatin or capecitabine; capecitabine with cisplatin or oxaliplatin; fluorouracil with cisplatin or oxaliplatin; and single-agent fluorouracil, capecitabine, and gemcitabine are included. Second-line chemotherapy is not recommended due to insufficient evidence of the efficacy. In unresectable but nonmetastatic disease, fluoropyrimidine chemoradiation can be another option. In addition, patients with intrahepatic cholangiocarcinoma, locoregional therapy such as external beam radiotherapy, and arterially directed therapy can be tried with a category 2B recommendation.

ESMO clinical practice guidelines suggest a combination therapy for performance score (PS) 0–1 patients and monotherapy for PS 2 patients with advanced cholangiocarcinoma [23]. According to the guidelines, cisplatin/gemcitabine is the reference regimen for good PS patients, and oxaliplatin may be substituted for cisplatin with concern about renal function. For PS 2 patients, gemcitabine monotherapy may be considered. And, second-line chemotherapy and targeted therapies are not recommended due to lack of evidence. Radiotherapy may be considered in patients with localized disease, and radioembolization may be considered in inoperable intrahepatic cholangiocarcinoma.

5. Future directions

5.1. Precision medicine

Personalized therapy is noticed in recent periods including target therapy and immunotherapy, in addition to systemic chemotherapy or chemoradiation for cholangiocarcinoma. Understanding of the molecular pathways associated with development and progression of cholangiocarcinoma may help identify novel biomarkers and develop potential therapeutic targets. On the basis of the development of gene sequencing technic, it is expected that precise medicine will be possible by judging the presence or absence of a specific gene expressed in a patient and selecting a therapeutic drug according to gene expression.

So far, most of previous studies have studied cholangiocarcinoma and gallbladder cancer as a group of biliary tract cancers; however, recent studies revealed that molecular profiling of cholangiocarcinoma is different from gallbladder cancer. Furthermore, several studies reported that intrahepatic and extrahepatic cholangiocarcinomas have different molecular features. Jusakul et al. reported the research combining whole-genome sequencing and epigenomic analysis of cholangiocarcinoma with 489 patients from 10 countries [58]. In the study, cholangiocarcinoma was subgrouped into four clusters according to their molecular features. Cluster 1 comprised mostly fluke positive tumors with enrichment of ARID1A and BRCA1/BRCA2 mutations. Cluster 2 was characterized by a mix of fluke positive and negative tumors with upregulated CTNNB1, WNT5B, and NKT1. Clusters 1 and 2 were enriched in TP53 mutation and ERBB2 gene expression. Clusters 3 and 4 were mostly fluke negative tumors, and cluster 3 exhibited specific upregulation of immune checkpoint genes, PD-1, PD-L2, and BTLA. Cluster 4 had BAP1, IDH1/2 mutations, and FGFR alterations.

Anatomical classification of cholangiocarcinoma was associated with clusters. Clusters 1 and 2 were enriched in extrahepatic tumors, whereas clusters 3 and 4 consisted almost of intrahepatic tumors. Moreover, intrahepatic cholangiocarcinoma was more frequently mutated in BAP1 and KRAS. Clinically, each clusters had different overall survivals; clusters 3 and 4 had significantly better overall survival than clusters 1 and 2. These findings suggest that heterogenic clinical features of cholangiocarcinoma were also based on genetic and epigenetic variance of tumors, and further studies have to focus on classifying subgroups according to treatment strategy and identifying novel therapeutic targets for personalized therapy.

5.2. Identifying novel biomarkers as therapeutic targets

To establish reliable strategy for precision medicine, it is important to identify novel molecular pathways and develop them as therapeutic targets. Recent studies developed growth factor receptors and signaling pathways as targets of cholangiocarcinoma. As mentioned above, the EGFR/VEGF inhibitors and multi-kinase inhibitors have been evaluated to be treatment options. Other promising signaling pathways associated with cholangiocarcinoma, such as RAS/RAF/MEK and PI3K/AKT/mTOR pathways, are also being studied to be another candidate of target agents. Clinical trials and researches are needed to find new target and evaluate efficacy of novel target agents. Big data analysis and artificial intelligence technologies are expected to reduce the time and effort required to set new molecular targets.

5.3. Immunotherapy

Advances in knowledge of cancer immunology provide opportunity of immunotherapy as a new therapeutic option for cholangiocarcinoma. Immunotherapy strengthens the immune system of patients to struggle against cancer by the concept of personalized vaccination, adoptive immunotherapy, or immune checkpoint inhibitor therapy. One of the immune checkpoint inhibitors, pembrolizumab, which is a blocker of programmed cell death 1 (PD-1) pathway and its ligands (PD-L1 and PD-L2), has been reported as a possible promising antitumor agent in patients with advanced biliary tract cancer in the interim results of the clinical trial, KEYNOTE-028. In the study, objective response rate was 17% (four has partial response and four had stable disease) [59]. In addition to the immune checkpoint inhibitor, NK cell, T cell, and dendritic cell-based therapies have been tried to treat cholangiocarcinoma. In the future, immunotherapy might be a new treatment option of biliary cancer treatment.

5.4. Ongoing clinical trials

Although there are no clear results yet, efforts to find new effective chemotherapy regimen for cholangiocarcinoma are continuing. There are several interesting ongoing clinical trials of chemotherapy for cholangiocarcinoma.

For the first-line chemotherapy for advanced cholangiocarcinoma, a phase III study comparing gemcitabine plus cisplatin/S1 combination to gemcitabine plus cisplatin combination is

under investigation (NCT02182778). For the second-line chemotherapy for advanced disease, a phase III trial of mFOLFOX regimen comparing to the best supportive care is ongoing (ABC-06 study, NCT01926236), and another phase III trial is trying capecitabine with varlitinib, an inhibitor of tyrosine kinases—EGFR, HER2, and HER4—compared to capecitabine alone (TreeTopp study, NCT03093870), Also, there is a phase III trial of adjuvant chemotherapy after curative resection with gemcitabine and cisplatin compared to observation alone (ACTICCA-1 trial, NCT02170090).

In addition to these phase III trials, various phase II/phase II trials are underway and expected to report encouraging results in the near future.

5.5. Other challenges

Overcoming disease heterogeneity is another important issue for physicians and researchers. As we discussed, biliary tract cancers have many subgroups according to anatomy and molecular features. In addition to relative rarity of cholangiocarcinoma, this heterogeneity has made clinical trials be small size and segmental. It is very difficult to draw integrated results from individual studies due to these heterogeneity characteristics of cholangiocarcinoma. In the future, it will be necessary to carry out multicenter and international cooperation to conduct large-scale clinical trials with subgroups sharing homogeneous characteristics.

Sample acquisition is one of the challenging tasks in pancreatobiliary tumor. If the future of technology including artificial intelligence allows us to perform more accurate sample acquisition technics or on-site mutation analyses easily, there will be significant benefits for diagnosis and treatment for these fatal diseases. And, established preclinical models need to identify new biomarkers and predict treatment response to chemotherapy. In addition to animal model, in vitro humanlike cell culture methods, such as organoid model or conditionally reprogrammed cell culture, are now being actively studied. These efforts will lead us to the era of precision medicine.

6. Summary and conclusion

Cholangiocarcinoma is a rare malignant tumor that originates from the epithelial cells of the bile duct system. While only surgical resection can provide a cure, most of cholangiocarcinomas are detected at inoperable stage and associated with poor prognosis. Moreover, cholangiocarcinoma has high recurrence rate, even after curative surgery.

Adjuvant chemotherapy is effective in patients with cholangiocarcinoma after curative surgery, especially with lymph node-positive and resection margin-positive disease. Although there are limited clinical trial data to establish a standard chemotherapy regimen for cholangiocarcinoma after surgery, current recommended regimens are fluoropyrimidine-based or gemcitabine-based chemotherapies.

Palliative chemotherapy has an important role in the treatment of advanced and recurrent cholangiocarcinoma. According to the results of randomized controlled phase III trial,

gemcitabine plus cisplatin combination became the standard treatment option for first-line chemotherapy of advanced and metastatic cholangiocarcinoma. Gemcitabine-based or fluoropyrimidine-based combination chemotherapies can be other options. The efficacy of second-line chemotherapy is not definite until now.

Precision medicine is noticed in recent periods in addition to cytotoxic systemic chemotherapy or chemoradiation. Identify novel therapeutic targets based on next-generation sequencing technology, and immunologic assessment is actively taking place. In the future, anticancer therapy of cholangiocarcinoma will develop to identify specific genes expressed in individual patients and provide personalized therapies accordingly.

Conflict of interest

There is no conflict of interest to declare.

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Chapter 4

Multidisciplinary Approach of Malignant Tumors of the Biliary Tree

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Additional information is available at the end of the chapter

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Abstract

Biliary tract carcinomas are aggressive tumors that arise from epithelial cells of bile ducts. They present several difficulties in their clinical management. A late initial diagnosis (frequently in the form of locally advanced disease), jaundice, cholangitis, or poor performance status of patients are some of the medical issues that arise in this setting. Another clinical limitation is the lack of robust evidence for many of the standard procedures in this particular scenario. Biliary tumors are lethal tumors, and most of them present in the form of advanced disease or during late evolution. However, we are witnessing some exciting changes in clinical management of tumors of the biliary tract, such as the development of new radiological techniques and novel interventional radiology procedures, the emergence of new radiotherapy modalities, the establishment of standardized chemotherapy regimens, the advance in molecular knowledge, and the development of new treatments directed against therapeutic targets. On the other hand, the most important step for advancing the treatment of these complex diseases is the appearance of multidisciplinary management teams integrating qualified specialists to resolve appropriate treatment challenges. In this chapter, we summarize the most relevant advances in clinical management and new oncologic treatment in biliary tract carcinomas.

Keywords: biliary tract cancer, cholangiocarcinoma, multidisciplinary targeted therapy

1. Introduction

Biliary tract carcinomas are rare and highly lethal tumors that arise from epithelial cells of bile ducts. Bile duct carcinomas are divided into extrahepatic and intrahepatic carcinomas, and

most of them are locally advanced tumors at presentation. Intrahepatic tumors were classified typically as primary liver cancer, while extrahepatic tumors were traditionally divided into cancers of the gallbladder, the extrahepatic ducts, and the ampulla of Vater.

Usually, the term of cholangiocarcinoma has been used to describe bile duct cancers arising in the intrahepatic, perihilar or distal (extrahepatic) biliary tree, exclusive of the gallbladder, or ampulla of Vater. In general, perihilar disease represents 50%, distal disease 40%, and intrahepatic disease less than 10% of biliary tract cases [1].

Clinically, bile duct tumors can manifest different clinical presentations, mainly on the basis of the initial growth site. Thus, tumors of the intrahepatic biliary tract appear as locally advanced hepatic mass with or without satellite lesions, and mimic isolated metastases from the other primary sites, or they can pose a differential diagnosis with the other primary hepatic tumors, mainly with hepatocellular carcinoma (HCC). Gallbladder tumors can be difficult to differentiate from abscesses or be a part of an atypical choledocholithiasis evolution. Proximal biliary tumors may be morphologically similar to pancreatic head cancer and cholangiocarcinomas distal to duodenal tumors. The profile of serum tumor markers (especially CA 19.9), the morphology, and especially the pathological anatomy data are the key to its final diagnosis.

Incidence data worldwide are difficult to evaluate because intrahepatic and extrahepatic tumors are included in separate categories. Intrahepatic bile duct carcinomas are usually assigned as primary liver tumors, while extrahepatic duct carcinomas are independent entities rather than grouped gallbladder cancers. In the United States, gallbladder and other extrahepatic bile duct tumors represent 12,190 estimated new cases and 3790 estimated deaths for 2018 [2]. Some studies suggest that only 15% of biliary tree tumors are intrahepatic cholangiocarcinomas [3], a minimal proportion of 42,000 new cases and 32,000 deaths of primary liver tumors in this period.

Bile duct tumors in recent years have undergone several relevant modifications regarding their staging. Importantly, the newest version of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) Cancer Staging Manual differs in their definitions of T stage and the prognostic stage groupings [4]. Some of these changes in this newest version (2017) improved the prognostic stratification of the TNM staging system [5] and presented notable implications for interpretations and comparison of outcomes from trials and retrospective series that used older TNM staging criteria [6].

Tumors of the bile duct are entities that present many limitations in their clinical management. Globally, cholangiocarcinomas present with a marked poor prognosis and several difficulties in their initial diagnosis, frequently in the form of locally advanced disease, jaundice, cholangitis, or poor performance status of patients. On the other hand, the need for sophisticated diagnostic methods often includes the need for insertion of biliary stents that normalize bile flow, which increases cost and risk of severe complications. Similarly, surgery in cases of localized disease presents a relevant postsurgical morbidity and mortality. The management of locally advanced tumors is poorly defined, while disseminated tumors have a lack of effective treatments. For all of these reasons, bile duct tumors are a clinical challenge that requires specialized centers for proper management. The creation of multidisciplinary teams is mandatory to optimize the knowledge of each specialist in each field.

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Treatment of bile duct tumors is based on localization (intrahepatic, gallbladder, distal, perihilar, or proximal tumor), staging (potentially resectable, locally advanced—unresectable and advanced tumors), and the patient's general state at diagnosis (including liver function). Currently, we lack prognostic or predictive biomarkers of response whose optimizing decisions in clinical management of these tumors. Efforts should be directed toward improving and optimizing the clinical guidelines with which relevant clinical decisions are made.

In this chapter, we summarize the most relevant advances in the clinical management and the treatment of bile duct carcinomas. In recent years, there has been a great variety of novelties in diagnosis management (especially new radiological techniques, vascular radiology, and nuclear medicine) and therapeutic (including the best knowledge of the molecular biology of cholangiocarcinoma and relevant advances in immunotherapy, liquid biopsy, or targeted therapies) that we will review in the following sections.

2. New radiological techniques

2.1. Abdominal ultrasound

Ultrasound is the initial modality of choice to evaluate the liver and biliary system frequently due to decreased associated cost, quick access, and no radiation. The assessment of biliary ductal dilatation is excellent with standard ultrasound given its satisfactory sensitivity of 85–95% [7]. However, just as clinically indicated, it is difficult to distinguish between cholestatic jaundice caused by benign entities and malignant etiologies, and standard ultrasound also suffers from some limitations. In the setting of a dilated biliary system and clinical suspicion for malignancy, the sonographer must perform a detailed scan of the liver parenchyma. Unfortunately, even with a detailed examination, standard ultrasound examination only results in correct diagnoses of benign lesions in 26–35% of cases and 28–39% in malignant lesions [8]. Contrast-enhanced ultrasound imaging thus represents a breakthrough in increased detection of hepatobiliary malignancy. With contrast-enhanced ultrasound, detection of malignant lesions is comparable and sometimes superior to those of contrast-enhanced computed tomography or magnetic resonance imaging, with sensitivity and specificity at 88 and 81%, respectively [9]. Notably, this requires advanced equipment fitted with a low-mechanical index option and pulse-inversion harmonic imaging in order to not degrade the microbubbles of the intravenous contrast agent. A contrast-enhanced examination typically utilizes three phases of contrast including arterial (early) phase at 15–35 s post injection, portal phase at 35–90 s, and delayed venous phase at 90–240 s [7]. A final limitation of ultrasound is the fact that it is very experience-dependent when compared with CT and MRI examinations, thus requiring a well-trained ultrasonographer for optimal results. Ultrasound is also not as accurate as CT and MRI with regard to the estimation of tumor spread and tumor resectability [10]. Thus, ultrasound is often used for initial evaluation to determine the next appropriate imaging modality of choice.

Endoscopic retrograde cholangiopancreatography (ERCP) was previously the standard established procedure for working-up patients with obstructive jaundice. Given its invasive characteristics and inherent complication rate of 3–9% and mortality of 0.2–0.5%, other modalities such as MRCP have become the initial test of choice [11]. ERCP is now almost exclusively used in a therapeutic role and not in initial diagnosis. However, when ERCP is used, endoscopic ultrasound (EUS) can be used as an adjunct procedure to detect and stage periampullary neoplasm and for ultrasound-guided fine needle aspiration.

2.2. Computed tomography

Although utilizing radiation, computed tomography (CT) is an excellent modality to assess the biliary tract given its quick acquisition and thus patient tolerance. Contrast-enhanced CT is highly accurate in the detection of biliary ductal dilatation and is easily used in this setting of a dilated biliary system. The normal common bile duct and common hepatic duct diameter are generally less than 7 mm with imperceptible or barely visible wall at the time of CT imaging [12]. The normal intrahepatic ducts should only be faintly seen at the time of contrast-enhanced CT imaging; if they are visualized, further search should be initiated as the differential includes proximal benign stricture, inflammation, biliary tract stones, or neoplasm. Distinguishing benign from malignant strictures can often be difficult, but, in general, malignant neoplasms demonstrate irregular, eccentric shouldering at the transition point from normal caliber to dilated ducts [12]. Benign strictures often demonstrate smooth, uniform narrowing as the ductal system transitions from normal caliber to dilated ducts [6]. Once biliary neoplasm is suspected, a multiphase contrast-enhanced CT approach is the key as cholangiocarcinoma is best discovered on delayed phase imaging (10–20 min, for example) with retention of contrast material in 40% of cholangiocarcinomas when compared with the normal surrounding liver parenchyma [12].

One of the major goals of imaging, particularly with CT, is to establish the presence or absence of satellite nodules or distant metastases, also identifying the relationship of the tumor to the biliary tree, hepatic vasculature, and the inferior vena cava [13]. CT is also useful to perform volumetric assessment, which allows evaluation for viable potential liver remnants if patients are considered for surgical resection. Extrahepatic disease evaluation is also importantly evaluated, often with a contrast-enhanced CT examination of the chest, abdomen, and pelvis. Limitations of CT include underestimation of longitudinal and proximal extent of the tumor and a sensitivity of only 54% for regional adenopathy. Other limitations include streak artifact and secondary inflammatory changes, which occur in the setting of patients with biliary stents [13].

2.3. Magnetic resonance imaging

Magnetic resonance imaging (MRI) is an excellent modality for the assessment of the biliary system due to its lack of ionizing radiation and excellent contrast resolution. MRCP is considered the radiologic modality of choice in the evaluation of patients with suspected cholangiocarcinoma given its accurate ability to map the biliary tree without requiring instrumentation [13]. MRCP takes advantage of the relatively high-signal intensity of static fluids in the biliary

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tract with heavily T2-weighted sequences, resulting in excellent contrast given the associated low signal of the remaining background tissues [12]. It achieves better evaluation of peripheral ductal involvement in cholangiocarcinoma given that an obstructing tumor will often not allow the more peripheral ducts to be adequately be filled during ERCP [13].

The previously long-imaging times for MRCP have been diminished by the use of short-breath hold T2-weighted acquisitions, parallel imaging, and sophisticated respiratory triggering mechanisms [12]. Utilizing a 1.5 Tesla strength magnet scanner or greater and modern multichannel surface coil technology also shortens the imaging times. T1-weighted images with and without gadolinium contrast are performed as well, particularly in the staging of biliary malignancies. 3D isotropic MRCP is often utilized to improve visualization of the intrahepatic bile ducts, allowing thinner sections without intersection gaps and the ability to manipulate the images into any projection for surgical planning [12].

MRI hepatobiliary-specific contrast agents are a particular advantage for imaging the biliary system. These initially distribute in the extracellular fluid compartment, thus providing initial excellent vascular evaluation during the arterial and portal venous phases. They are also actively taken up by the hepatocytes and excreted into the bile, providing excellent imaging of the biliary system on more delayed imaging. These agents are separated into two main categories: manganese-based (mangafodipir trisodium, Teslascan®) and gadolinium-based (gadobenate dimeglumine, MultiHance® and gadoxetic acid, Primovist® in Europe and Eovist® in the United States) agents [13].

2.4. Interventional radiology

In cases of malignant biliary obstruction, interventional management may be indicated. Percutaneous biliary drainage can be performed to decrease serum bilirubin levels, which may facilitate medical therapy, chemotherapy, or possible surgical interventions. However, not all patients may be good candidates for this procedure and preprocedural total serum bilirubin levels, international normalized ratio (INR) and the degree of biliary drainage should be utilized as prognostic factors for subsequent patient selection [14].

Before considering biliary intervention, appropriate cross-sectional imaging should be performed such as thin-slice computer tomography (CT) and magnetic resonance (MR) imaging with MR cholangiopancreatography (MRCP) protocol. Low bile duct obstructions can frequently be managed by using a single catheter or stent across the obstruction through endoscopic retrograde cholangiopancreatography (ERCP). Conversely, high bile duct obstruction involving the confluence or more proximal ducts may not be amenable to such a procedure. Depending on the unique circumstances of each case, interventional procedures such as percutaneous cholangiography, percutaneous transhepatic biliary drainage (PTBD), stent placement, and bile duct biopsy may need to be performed [14].

2.5. Nuclear medicine in biliary tree tumors

Positron emission tomography (PET) appearance in the clinical practice scenario has been revealed as a usefulness advancement in the staging and clinical management of a wide

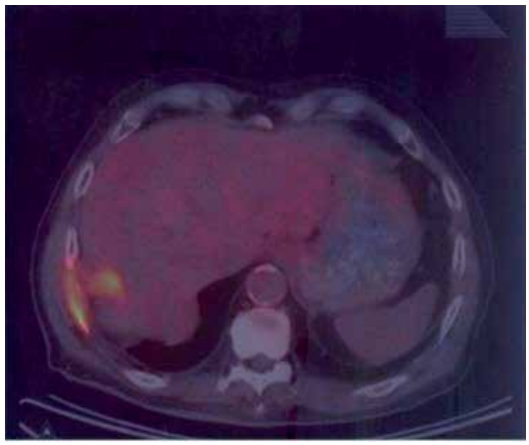

Figure 1. Positron emission tomography. Biliary tract relapse on a drainage sinus scar.

variety of tumors, such as colon cancer, lung cancer, melanoma, and many others. However, the role of PET in bile duct tumors is not well defined. Clinical studies focused on the value of the extension study in potentially resectable tumors, both intrahepatic cholangiocarcinoma and cholangiocarcinoma, gallbladder cancer or common bile duct cancer [15, 16]. Preliminary studies point to some utility in the neoadjuvant setting. It seems to be a technique especially useful in the detection of affected lymph nodes. The value of the high SUV-max glucose uptake is also associated with an unfavorable prognostic value [15]. Local or distant tumor relapse detection by PET during clinical surveillance after radical resection has been described [17], but the value for this setting needs to be developed (**Figure 1**).

3. Surgical approaches

3.1. Management of resectable bile duct carcinomas

Surgical resection of bile duct tumors is the only curative treatment in these tumors. Distal cholangiocarcinomas have the highest rates of resection, while proximal tumors have the lowest rates (particularly, perihilar neoplasms) [16–18]. Resection rates of distal, intrahepatic, and perihilar lesions are 91, 60, and 56%, respectively [19], in some studies. Even in patients who undergo potentially curative resection, margins free of tumor involvement can be obtained in only 20–40% of distal tumors and 50% of distal tumors [20]. A tumor-free proximal margin of at least 5 mm is necessary, so the series presented with these criteria are markedly low; this is an important issue because resection with margins is the only curative procedure [21]. Therefore, although surgical resection remains the gold standard for this disease, it is not so frequent to obtain long-term survival due to frequent postoperative recurrences [22, 23].

The main clinical requirements for resectability are absence of distant hepatic metastases or disseminated disease, absence of retropancreatic node metastases involvement, absence of

portal vein invasion or major hepatic artery (although in many oncological centers, where our institution, en-bloc resection with vascular recovery can be considered), and the absence of invasion of adjacent extrahepatic organs [24].

Patients with positive margins after resection or regional lymph nodes should have been prepared for adjuvant chemotherapy based on 5FU as well as radiation. Unfortunately, no randomized trials that support a standard regimen are defined. People with negative margins after surgery and negative involvement of the lymph nodes can be observed or treated with adjuvant strategies [25]. Radiotherapy and postoperative chemotherapy as clinical options in this setting are discussed in the following sections.

3.2. Computer-assisted surgery

Robotic surgery or robotically assisted surgery refers to technological developments in base to robotic systems aiding the surgical interventions, overcoming the surgical limitations, and enhancing the capabilities of surgeons performing traditional surgery. There are several theoretical advantages of robotic surgery: possibility of surgeries under remote control, improvement in precision procedures, minimum invasion, and lower postoperative morbidity.

The use of robotic surgery in tumors of the bile duct is currently considered to be nonstandard of care procedure. We can mention some theoretical limitations: surgical procedures need optimal software services and marked efforts for coordination among other specialist (i.e., pathological evaluation). Other limitations could be the high cost and the complexity of surgeon's training.

3.3. Orthotopic liver transplantation

Orthotopic liver transplantation is an option that should be considered, exceptionally, generally in highly selected proximal cholangiocarcinomas in combination with neoadjuvant treatment. Only a minority of patients will result in their eligibility, due to the restrictive criteria for their inclusion and the availability of liver transplant programs [26].

Selection criteria include the presence of a tumor without the possibility of a wide margin of resection, a good liver function, and the absence of metastasis (intra- or extrahepatic). These patients frequently begin their treatment with EBRT with concurrent chemotherapy 1–3 months; during a period, it is possible to demonstrate the absence of rapid systemic dissemination. Some clinical series offers remarkable survival rates [27]. However, its complex management and the restrictive conditions for participation make difficult to interpret the real benefit of this technique in overall management of bile duct patients.

3.4. Follow-up after resection and diagnosis of loco-regional relapse

No clear guidelines exist for follow-up after surgery in this particular tumor type. A reasonable approach seems to be physical exam with routine laboratory tests every 3–4 months for the first 3 years post-surgery and subsequently at longer intervals of 6 months until Year 5. The role of CA 19-9 level in surveillance is not clear, but persistently, rising levels often

precede radiological evidence of recurrence by a number of months. Therefore, this marker has been routinely incorporated in follow-up schemas. Which imaging tests to be performed is a topic that has not been specifically addressed in prospective trials, although CT scans of the abdomen every 6 months for 2–3 years after surgery are probably the most common approach in routine practice. However, depending on the case presented, CT and abdominal ultrasound are often not sufficient to detect loco-regional relapses, which could be easily determined on MRI and PET.

While recurrence is mostly loco-regional in the majority of proximal tumors, distal cholangiocarcinomas recur frequently at distant sites including the liver, peritoneum, and lung [28, 29]. Like pancreatic, gallbladder, and hepatocellular cancers, adenocarcinomas of the bile duct have a predisposition to seed and can recur in needle biopsy tracts, abdominal wall incision wounds, and the peritoneal cavity, and therefore, it is recommended to be especially careful in the physical exams of each follow-up visit [17].

3.5. Clinical management of loco-regional relapse

The ideal management of loco-regional relapse still remains undefined. No prospective data exist to set definitive recommendations about the optimum treatment after a curative resection of adenocarcinoma of the extrahepatic bile ducts. Currently, decisions are made based on different clinical parameters that have been established as prognostic factors in retrospective series, such as tumor grade, surgical margins, or lymph node involvement.

Surgery is generally not indicated for recurrent bile duct adenocarcinoma due largely to the location of recurrence, technical difficulty, frequent distant metastases, and aggressiveness. However, in patients with prolonged relapse-free interval and favorable location, surgery should be an option to consider [17]. Radiotherapy and systemic chemotherapy will be commented in the following sections.

4. Radiotherapy

4.1. Radiation techniques

Historically, radiotherapy was used in patients with locally unresectable advanced bile duct tumors as a palliative treatment in search of local control. However, a measurable benefit of radiotherapy treatment in terms of survival in this setting has not been well established [30, 31] because of a small size and retrospective design of the studies.

New advances in technology and improvements in safety and effectiveness may have resulted in some benefit using radiotherapy in locally or locally advanced disease. In addition, the improvement in imaging techniques has allowed a more precise planning in the treatment of upper gastrointestinal tumors. Specifically, in the last decade, treatments have been optimized based on the new EBRTs, such as 3D conformational radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT). IMRT uses computer-generated images to evaluate the

size and shape of the tumor mass, generating different intensities of radiation in base to a multiple-angle emission, reducing damage of normal tissues near the tumor.

Studies with accelerated or hypofractionated regimens (i.e., stereotaxic body radiation therapy—SBRT) have been tested in cholangiocarcinoma. SBRT is defined as an external beam radiotherapy method used to deliver a high dose of radiation therapy to an extracranial target using single or small number of fractions. Those treatments have also been tested in patients in the adjuvant setting. However, the difficulty in grouping cases in large and comparative clinical trials is a limitation to obtain definitive conclusions from standardized procedures.

4.2. Adjuvant and neoadjuvant therapy

At present, the role of neoadjuvant treatment prior to surgical resection is considered experimental. No comparative study has shown a survival benefit or an improvement in resectability in this setting. Safety data are not well defined. Neoadjuvant therapy in cholangiocarcinoma is a field open to research. The theoretical basis of neoadjuvant treatment offers several attractive advantages in the clinical management of bile duct tumors. Bile duct carcinomas present a high local recurrence rate (even in the context of disease-free surgical margins) and frequently preset systemic metastases. Neoadjuvant treatment would allow a theoretical biological control of the initial micrometastases, a "screening" of the responding patients with a selection of patients who would rapidly progress to treatment. Finally, the pathological evaluation of the tumor piece after the response to the preoperative treatment could be an excellent prognostic marker of the disease, as it happens in the majority of tumors where neoadjuvant treatments are used in a habitual way, as in rectal cancer.

On the other hand, the role of postoperative radiotherapy or chemoradiotherapy treatment versus chemotherapy alone in patients with resection of bile duct tumors has not been clearly defined. In general, preliminary studies offer hopeful results, generally with complementary radiotherapy compilation with single-agent therapies. The same considerations should be made with intraoperative radiotherapy.

4.3. Therapy for locally advanced disease

Locally advanced bile duct cancer is especially difficult to treat. In many cases, conclusions are based on studies that grouped patients with locally advanced adenocarcinoma of the pancreas. Globally, locally advanced bile duct tumors are treated in a similar way. Locally advanced unresectable tumors, especially symptomatic masses, can benefit from palliative EBRT. Usually, the treatment is combined simultaneously with single-agent chemotherapy (5-fluouracil, capecitabine). Treatment is usually continued either after the end of treatment or after the progression of disease with palliative chemotherapy (see next section).

Currently, the optimal sequence of treatment in locally advanced disease is unknown: chemotherapy as a first step (also called "induction chemotherapy") and then radiotherapy with

or without concomitant chemotherapy, or radical radiotherapy, or initial radical chemoradiotherapy. Neither is known the real therapeutic value of surgery after radical radiotherapy treatment, and what is the contribution of maintenance chemotherapy in this setting. All these questions must be answered with studies during the following years.

5. Chemotherapy

5.1. Adjuvant chemotherapy

Chemotherapy administration after resection of bile duct tumors is controversial. The evidence of benefit in intrahepatic tumors is very limited. The most important studies include tumors of the extrahepatic bile duct along with pancreatic cancer and use of single-agent chemotherapy schemes (5'fluouracil plus leucovorin, capecitabine, gemcitabine) with a marginal or no significant benefit.

At the present time, after complete curative surgical resection, clinical options are observed without treatment, chemotherapy (usually with single-agent chemotherapy as fluoropyrimidines or gemcitabine for 4–6 months) or chemoradiotherapy (discussed in detail in the next section). The results of meta-analysis are conflicting, although patients with node-positive and margin-positive tumors seem to benefit from treatment with chemotherapy alone or chemoradiotherapy.

5.2. Hepatic artery-based therapies

The rationale of hepatic artery-based therapies is based on the knowledge of the blood flow in the liver parenchyma, which is made from the hepatic artery rather than the portal vein. Thus, selective catheterization may be performed with the infusion of particles with embolization capacity or with cytotoxic chemotherapy infusions into the branch of the hepatic artery that feeds the tumor mass (TACE—transarterial embolization). This technique has had a broad development in hepatocellular carcinoma (HCC) and is an option to be considered in intrahepatic cholangiocarcinomas, although with less evidence. The administration of radioisotopes is also well defined in HCC. At present, there are no comparative studies among all the different procedures and techniques.

5.3. Chemotherapy in advanced disease

Systemic chemotherapy provides a modest benefit in the treatment of advanced biliary tract carcinomas. At present, cancer of the bile duct is considered an incurable and progressive disease with few cases whose median survival is greater than 1 year. There is a wide variety of chemotherapy treatments for advanced disease. The different combinations try to adapt to a great variety of factors such as different locations, presence or absence of previous treatments, performance status condition of the patient, and the remaining liver function.

Most of the drugs used in this setting are commonly used in other tumors of the upper gastrointestinal tract and have some activity on these tumors: gemcitabine, fluoropyrimidines (i.e., combinations of 5'fluouracil and leucovorin, capecitabine), platinums (usually oxaliplatin),

irinotecan, and anthracyclines. In general, single-agent therapy is usually used for people with poor prognosis or poor performance status, while those of good performance status are usually treated with chemotherapy combinations.

The most commonly used treatment is the combination of gemcitabine plus cisplatin. The treatment has shown a superior overall survival [32] in comparison to treatment with single-agent gemcitabine (11.7 versus 8.1 months) with an acceptable toxicity profile. However, the treatment is not compared with other combinations, also active. Randomized trials will be necessary to determine if this is the standard regime.

Second-line treatment lacks robust evidence. In routine clinical practice, progression to gemcitabine-based treatment is usually treated with fluoropyrimidine-based chemotherapy (oxaliplatin plus leucovorin/5-fluouracil, the FOLFOX regimen).

Initially, any patient with locally advanced incurable bile duct tumors or disseminated tumors should be considered for entry into a clinical trial. Within the standard choice, this has to be a priority, due to the poor prognosis and the lack of curative treatments in this setting. The possibility of genomic sequencing is a fact, and many of the major oncological treatment centers in the world are initially offering the possibility of such studies within the usual clinical practice. Unfortunately, at the present time, there are no specific treatments available for any molecular target in the bile duct in routine clinical practice; in addition, some targets have been tested in other biologically similar tumors but not in biliary tumors. However, not all the entire theoretical therapeutic targets have associated a new molecule or drug in development. Despite all these, the need for researchers, physicians, and patients to initiate innovative studies to improve the prognosis of these tumors is mandatory.

6. Targeted therapy

6.1. Molecular basis

Bile duct carcinoma is one of the most interesting gastrointestinal tumors in terms of genomic alterations, as it has been shown in different publications since 2013. However, results of targeted therapy for these alterations have been quite disappointing. Compared to other gastrointestinal malignancies such as gastric or colorectal carcinoma, no targeted drug has yet been approved in cholangiocarcinoma. Despite these poor results, some promising drugs are now being evaluated targeting different aberrations observed when whole exome sequencing is performed. It is remarkable that bile duct carcinoma should not be considered as a unique disease. Intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder carcinoma have a different molecular landscape, and this could explain the low rate of success of targeted therapy in these carcinomas.

One of the most relevant analyses in this field [33] based on a whole exome sequencing of 260 tumors from the biliary tract surprisingly revealed that almost 40% of cases harbored targetable genetic alterations comprising a total of 32 genes. Moreover, these genetic alterations differ among the different locations, as summarized in **Table 1**. A total of 137 intrahepatic

Tumor subtype	Alteration	Targetable
Intrahepatic cholangiocarcinoma	FGFR2 fusion	Yes
	IDH1/2 mutation	Yes
	EPHA2	No
	BAP1 mutation	No
Gallbladder carcinoma	EFGR mutation	Yes
	ERBB2 mutation	Yes
	PTEN mutation	Yes
	ARID 1 mutation	No
	MLL2/MLL3 mutation	No
	TERT promoter mutation	No
Extrahepatic cholangiocarcinoma	PRKACA/B fusion	Yes
	ELF3 mutation	No
	ARID1B mutation	No
Biliary duct common carcinoma	TP53 mutation	No
	BRCA mutation	Yes
	PI3KCA mutation	Yes

Table 1. Targeted therapies in biliary tract tumors.

cholangiocarcinomas, 74 extrahepatic cholangiocarcinomas, and 28 gallbladder tumors were analyzed. Main alterations can be classified under five different modules: MAPK pathway (RAS, BRAF, EGFR, ERBB2, FGFR, and PTEN), TFG-β pathway (TGF-B, SMAD4, and ARID), TP53 pathway (TP53, ATM, and MDM2), cell cycle regulation (CDKN2A/B, RB1), and epigenetics (IDH1, IDH2, and BAP1, among others) (**Table 1**).

A worldwide consortium analyzing the genome of different tumors (the Cancer Genome Atlas) has recently revealed a comprehensive study of intrahepatic cholangiocarcinoma based on somatic mutations, RNA expression, copy number, and DNA methylation [34]. Similarly, inactivating mutations have been found in tumor-suppressor genes, such as ARID1A, ARID1B, BAP1, TP53, and PTEN, and gain-of-function mutations have been found in the oncogenes, such as IDH1, IDH2, BRAF, and KRAS. Moreover, alterations in the regulation of the cell cycle have been reported: recurrent focal losses of CDKN2A, encoding p16INK4A, which inhibit the cyclin-dependent kinases CDK4 and CDK6, have been observed in 47% of the tumors.

6.2. Developing targeted therapies

Drugs targeting MAPK, FGFR, and IDH pathways have been developed widely in biliary duct carcinoma. One of the most prevalent alterations in cholangiocarcinoma is mutations in the proteins involved in RAF-MEK-ERK pathway. Targeting epithelial growth factor receptor

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(EGFR) as the first member of the MAPK pathway has not been successful. A phase III trial comparing platinum-based chemotherapy and gemcitabine with and without erlotinib did not show an improvement in progression-free survival [35]. Similar results were obtained with sorafenib (a multikinase inhibitor of RAF and VEGFR family) [36]. MET, a regulator of this pathway, can be inhibited by different drugs, such as tivantinib or cabozantinib. Despite preliminary efficacy of tivantinib combined with gemcitabine, cabozantinib (targeting MET and VEGFR2) showed limited activity [37–39].

KRAS mutation is observed in up to 25% of cholangiocarcinomas, and it has been associated to a worse prognosis in terms of progression-free survival and overall survival [40]. Targeting KRAS has been a challenge in oncology, and currently, there is not any available drug against it. However, it is possible to target downstream proteins, such as MEK. Selumetinib, an allosteric MEK inhibitor, was tested in advanced biliary cancer with good results as single therapy in refractory setting (progression-free survival around 3 months and overall survival of 9.7 months). This drug was also combined with standard first-line chemotherapy (cisplatin-gemcitabine), but results were quite modest. Nevertheless, there was no selection according to KRAS mutation [41]. BRAF mutations are less prevalent, but results with therapies targeting this protein have shown better results.

For instance, in the vemurafenib basket trial (BRAF inhibitor in BRAF V600E mutant tumors), there was a partial response of eight patients treated with this drug [42]. However, there was up to 62% rate of disease control. Combinations of BRAF inhibitor and MEK inhibitor such as dabrafenib and trametinib are now being evaluated in clinical trials (NTC02034110).

Fibroblast growth factor receptor (FGFR) has been suggested as a potential target in cholangiocarcinoma, especially in intrahepatic cholangiocarcinoma with 20% of them showing any alteration. Most frequent alterations are fusions and mutations in FGFR2 and FGFR3. Some selective and nonselective small-molecule inhibitors of this receptor have been investigated in early phase clinical trials. Preliminary activity of oral pan-FGFR inhibitor BGJ398 has shown a disease-control rate of 82% in advanced cholangiocarcinoma in a phase II study, which is still recruiting (NCT02150967) [43]. Similarly, erdafitinib showed a 91% disease-control rate in this setting [44], and a phase II is ongoing to confirm these results. Derazantinib is another multikinase potent inhibitor, with a potent pan-FGFR inhibition. In the phase I trial [45], a 20% response rate was observed in FGFR-2 fusion-positive cholangiocarcinoma. Stable disease was observed in another 48% of the patients [45, 46]. TAS-120, Debio1347, and ponatinib are also drugs targeting FGFR in early phase I trials.

Other alterations in cholangiocarcinoma are ROS1 fusions with some interesting results with ALK/ROS inhibitors, such as ceritinib. Similarly, entrectinib (targeting not only ALK/ROS but also NTKR) has shown encouraging responses.

As previously described, alterations in IDH1, IDH2, BAP1, and ARID1A are frequently observed in cholangiocarcinoma. These genes are considered epigenetic regulators, as they are responsible for remodulating chromatin and histone regulation. Therefore, drugs targeting epigenetic alterations could be a strategy in biliary tract carcinoma. The most frequent mutated gene is IDH1, a gene that encodes isocitrate dehydrogenase, responsible among

others, for the Krebs cycle or mitigating the oxidative stress. One of the most promising therapies is AG-120, a selective inhibitor of mutant IDH1. A 60% rate of disease control has been observed in a phase I trial. A phase III trial is now recruiting to confirm these results (NCT 02989857). Enasidenib is another IDH inhibitor, specific for IDH2 mutant tumors, which is currently being evaluated in another trial (NCT02273739). Other drugs that have been tested but without definitive results are histone deacetylase and DNA methyltransferase inhibitors.

7. Immunotherapy and cholangiocarcinomas

Treatment based on altering the immune response of the patient generating an intrinsic antitumor effect is supposed to have a new change of paradigm in the field of medical oncology. Several tumors have seen their therapeutic arsenal expanded and have benefited from incredible responses with a favorable toxic profile. It is a field in full scientific development, and poor prognosis tumors such as melanoma or nonsmall cell lung have been benefited.

Biliary tract tumors are infrequent tumors with low prevalence in Western Countries, which delay and complicate their recruitment in clinical studies. However, there are several clinical and biological characteristics of these tumors that make them attractive to the use of immunotherapy. These are tumors especially linked to chronic infection and inflammation processes, similar to other tumors with good immune responses (i.e., HCC or head and neck carcinoma). These are tumors with a high rate of presentation of neoantigens associated with viral infection.

At least one subgroup of patients with cholangiocarcinoma has a high mutational load with abundant neoantigens and a high expression of immune-related genes, including inhibitory-encoded genes. These are tumors with a poorer prognosis but with a good theoretical response profile to immunotherapy. New studies underway will delimit the role of these therapies in biliary tumors in the next few years. On the other hand, new therapies based on immune response are not exempt from possible high-risk secondary effects for these patients; cholangiocarcinomas often present a high risk of inflammatory life-threating complications (biliary stent, biliary superinfection).

8. Liquid biopsy: new steps toward better monitoring

Liquid biopsy (LqB) presents the possibility of detecting circulating tumor cells (CTCs) or small fragments of tumor DNA (cell-free DNA or cfDNA) in the circulatory system of patients, analyzing both primary tumors and metastases. This new technology has obvious advantages: it allows a global analysis of genetic changes in the global tumor mass, independently of the location of foci with independent genomic progression or novel mutations in isolated regions of the tumor tissue. LqB allows to study the tumor heterogeneity and to evaluate a dynamic tumor analysis over time, including the assessment of cancer-resistant subclone appearance,

and its results potentially predict the molecular dynamics associated with tumor response and drug resistance. Liquid biopsy monitoring of patients with cancer is a technically available procedure. However, our current knowledge should be expanded before it can be routinely implemented in daily clinical use.

Improvements have been made in technology, and there have been decreases in the response time and the costs of the procedure. In the near future, cancer research centers and even direct patient care centers will routinely request LqB for cancer patients using kits and genetic panels available. At this time, however, it is necessary to expand the available information about the LqB utility, especially the clinical interpretation of its results and limitations of the technique. Unfortunately, at this time, there are no studies that validate its usefulness in bile duct tumors.

9. Conclusions: multimodality approach

At present, we are witnessing some exciting changes in the clinical management of tumors of the biliary tract. Primarily, the development of new radiological techniques allows an earlier and more accurate diagnosis of these diseases; they also provide many anatomic and functional relevant information with a prognostic value. A critical advancement in nearly all of extrahepatic bile duct tumor management is the improvement in interventional radiology techniques, especially biliary stents in locally advanced disease. Their staging has improved a better global approach and more accurate prognostic allocation. The emergence of more accurate radiotherapy treatments can expand the indications of the most novel techniques, such as IMRT, in the near future. Standard chemotherapy regimens, although still with discrete results in advanced disease in terms of survival, allow the comparison with other

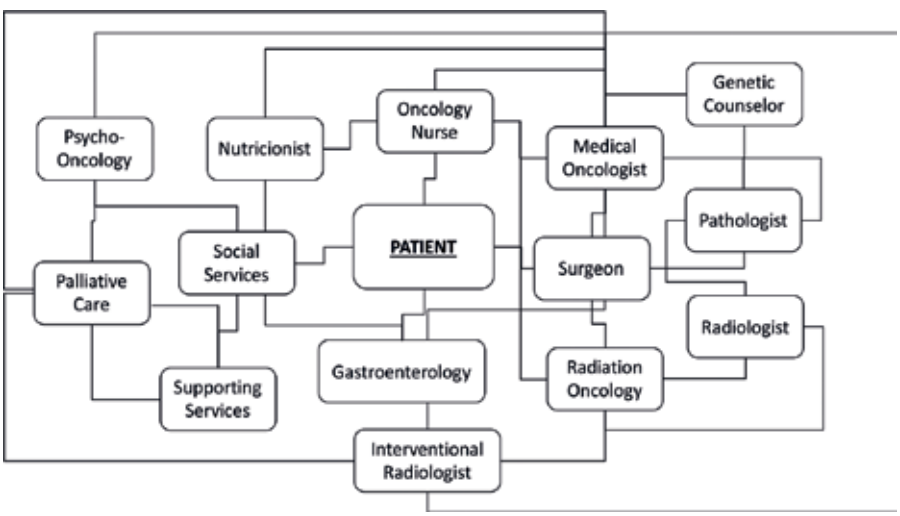

Figure 2. Multimodality approach in patients with biliary tract tumors.

novel treatments. Finally, the advancement in molecular knowledge is critical to understand the pathogenesis and for the development of new treatments directed against therapeutic targets.

However, the most important step yet for advancing the treatment of these complex diseases is the appearance of multidisciplinary management teams focusing on patient treatment in a comprehensive approach. It is critical for the development of new strategies to assess each case from the point of view of multiple specialists in reference centers that can integrate the careful work of qualified specialists. Similarly, the most appropriate treatment should respond to the variable disease evolution of each patient, both in the curative approach and in the advanced disease of worse prognosis.

Finally, it is very important to remember, as shown in **Figure 2**, that the treatment of a tumor as aggressive as cholangiocarcinoma in a patient needs the participation and use of psychological, spiritual, social, family, voluntary, economic, that should be considered in each center of each specific region, resources that exceed the realization of this article. Unfortunately, the current advances have not translated into a change in the natural history of these diseases.

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Biliary injuries

Chapter 5

Biliary Tract Injuries

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Additional information is available at the end of the chapter

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Abstract

Injuries of the biliary system are rare. They can broadly be divided into traumatic biliary injuries and iatrogenic biliary injuries. Former are usually part of associated abdominal trauma, blunt or penetrating, and latter are consequence of surgical, endoscopic or invasive radiological diagnostic or therapeutic procedures done in various liver, pancreatic or disorders or the part of upper gastrointestinal system. They occur more commonly than traumatic injuries but still are rare. Those injuries represent important aspect in healthcare system because of their complexity and diversity in management, associated morbidity and mortality and expenditure in healthcare systems. This chapter will put focus on those injuries, including their classification, etiology and mechanism of occurrence, clinical presentation, diagnosis, treatment options, postoperative complications, and, when iatrogenic injuries are concerned, methods for prevention of those injuries.

Keywords: bile duct injuries, blunt abdominal trauma, penetrating abdominal trauma, iatrogenic bile duct injury, biliary leak, biloma, hemobilia, laparoscopic cholecystectomy, open cholecystectomy, endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), percutaneous transhepatic cholangiography (PTC), hepatobiliary iminodiacetic acid (HIDA), choledohojejunostomy, hepaticojejunostomy

1. Introduction

Isolated traumatic injuries of the biliary tract are extremely rare. They can be divided into intrahepatic, which can further be arbitrarily subdivided into central or peripheral intrahepatic depending on their location within the liver, and extrahepatic biliary tract injuries which involve right and left hepatic duct, common hepatic duct, common bile duct, cystic

duct and gallbladder. Intrahepatic biliary injuries are invariably associated with liver trauma and should be viewed and managed through that spectrum while extrahepatic biliary injuries can be solitary or, more commonly, also associated with other organ injuries, mainly liver, pancreas and duodenum, in blunt or penetrating abdominal trauma. Injuries can also be combined requiring different approach in diagnosis and treatment. Treatment should be multidiscplinary, involving surgeon, interventional gastroenterologist and interventional radiologist and decisions should be made according to the clinical presentation and concurrent injuries since, to date, there is no treatment algorithm for these injuries.

Iatrogenic biliary injuries are most often caused during laparoscopic cholecystectomy, open cholecystectomy, other surgical procedures involving organs of upper gastrointestinal tract or rarely during other procedures, namely endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC). Bile leak is common for all these injuires. Other symptoms and clinical presentation varies greatly depending on the mechanism of injury and associated trauma. Also there are different treatment approaches which are dictated by the symptoms, diagnosis and clinical presentation. In this chapter injuries will be divided in categories mainly for academic purposes because most treatment options are somewhat similar, and secundarily, for early recognition, specificities and treatment modalities since they can overlap and individualized approach is necessary in proper diagnosis and management.

2. Classification

Traumatic injuries to the biliary system can be intrahepatic or extrahepatic. Intrahepatic can be further arbitrarily subdivided into central (those involving the proximal right and left hepatic or segmental ducts within 5 cm of the hepatic duct confluence) and peripheral (those within the hepatic parenchyma more than 5 cm from the hepatic duct confluence) [1]. Extrahepatic biliary injuries are those of right and left hepatic duct, common hepatic duct, common bile duct, cystic duct and gallbladder. They can be isolated, combined or, which is most common, also associated with trauma of other organs, mainly liver, pancreas and duodenum. Since intrahepatic biliary injuries cannot be distinguished from liver parenchyma injuries Organ Injury Scaling (OIS) from American Association for the Surgery of Trauma (AAST) classification of those injuries should be used (**Table 1**) [2]. For extrahepatic injuries AAST extrahepatic biliary tree injury scale should be used (**Table 2**) [3]. Management options should be weighted according this classification system, patient's general condition, and associated trauma.

Classification of iatrogenic biliary tract injuries is more complex and there are numerous classification systems and none of them is commonly accepted. Classification systems are those of Bismuth, Strasberg, Stewart-Way, Siewert, Amsterdam, Lau, Csendes, Neuhaus, Hanover and others. Most widely used are those from Strasberg in which Bismuth classification system is included (type E injuries) and classification form Stewart-Way. Some of them are summarized in tables (**Tables 3**–**8**). **Table 9**. shows all classifications systems by year of their publication. In **Pictures 1** and **2** most used classification systems are depicted.

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Grade[a]	Injury description
I Hematoma	Subcapsular, less than 10% of the surface area
Laceration	Tear of the capsule, less than 1 cm parenchymal depth
II Hematoma	Subcapsular, from 10 to 50% surface area; intraparenchymal, less than 10 cm in diameter
Laceration	1–3 cm parenchymal depth, <10 cm in length
III Hematoma	Subcapsular, less than 50% surface area or expanding; ruptured subcapsular or parenchymal hematoma
Laceration	Intraparencymal hematoma >10 cm or expanding
	> 3 cm parenchymal depth
IV Laceration	Parenchymal disruption involving from 25 to 75% of hepatic lobe or 1–3 Couinaud's segments within a single lobe
V Laceration	Parenchymal disruption involving more than 75% of hepatic lobe or >3 Couinaud's segments within a single lobe
Vascular	Injuries around veins; i.e., retrohepatic vena cava/central major hepatic veins
VI Vascular	Avulsion of the liver

[a]Advance one grade for multiple injuries, up to grade III.

Table 1. Liver injury scale.

Grade[a]	Injury description
I	Contusion of the gallbladder
	Contusion of the portal triad
II	Partial gallbladder avulsion from liver bed; cystic duct intact
	Laceration or perforation of the gallbladder
III	Complete gallbladder avulsion from liver bed
	Cystic duct laceration/transection
IV	Partial or complete right hepatic duct laceration
	Partial or complete left hepatic duct laceration
	Partial common hepatic duct laceration (≤ 50%)
	Partial common bile duct laceration (≤ 50%)
V	> 50% Transection of common hepatic duct
	> 50% Transection of common bile duct
	Combined right and left hepatic duct injuries
	Intraduodenal or intrapancreatic bile duct injuries

[a]Advance one grade for multiple injuries, up to grade III.

Table 2. Extrahepatic biliary tree injury scale.

Type	Bile duct injury
A	Injuries of the cystic or of the small bile ducts of the liver bed
B	Occlusion of an aberrant hepatic duct, of a part of the biliary tree, most commonly the right aberrant right hepatic duct
C	Sectioning without ligation of an aberrant right hepatic duct
D	Lateral injury of the primary bile duct
E1	Injury of the common hepatic duct more than 2 cm from the confluence
E2	Injury of the common hepatic duct less than 2 cm from the confluence
E3	Injury in the hepatic hilum with preservation of the confluence
E4	Injury in the hilum with involvement of confluence and loss of communication between the right and left hepatic ducts
E5	Injury to an aberrant right sectorial hepatic duct alone or associated with a concomitant injury to the primary hepatic duct

Table 3. Bismuth-Strasberg classification.

Class	Bile duct injury
I	Incision (incomplete transection) of the common bile duct
II	Lateral damage to the common hepatic duct with electrocautery or clip
III	Transection of the common bile duct or common hepatic duct
IV	Injury to or transection of the right hepatic duct or right segmental hepatic duct

Table 4. Stewart-Way classification.

Type	Criteria
A	Cystic duct leaks or leakage from aberrant or peripheral hepatic radicles
B	Major bile duct leaks with or without concomitant biliary strictures
C	Bile duct strictures without bile leakage
D	Complete transection of the duct with or without excision of some portion of the biliary tree

Table 5. Amsterdam classification.

Type	Criteria
1	Leaks from cystic duct stump or small ducts in liver bed
2	Partial CBD/CHD wall injuries without (2A) or with (2B) tissue loss
3	CBD/CHD transection without (3A) or with (3B) tissue loss
4	Rt/Lt hepatic duct or sectorial duct injuries without (4A) or with (4B) tissue loss
5	Bile duct injuries associated with vascular injuries

Table 6. Lau classification.

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Type	Criteria
A	Peripheral bile leak (in communication with the common bile duct)
A1	Cystic duct leak
A2	Bile leak from the liver bed
B	Occlusion of the common bile duct (or right or left hepatic duct)
B1	Incomplete
B2	Complete
C	Lateral injury of the common bile duct
C1	Small lesion (< 5 mm)
C2	Extended lesion (> 5 mm)
D	Transection of the common bile duct (or right hepatic duct)
D1	Without structural defect
D2	With structural defect
E	Stenosis of the common bile duct
E1	Short stenosis of the common bile duct (< 5 mm)
E2	Long stenosis of the common bile duct (> 5 mm)
E3	Stenosis at the confluence
E4	Stenosis of the right hepatic duct or segmental duct

Table 7. Neuhaus classification.

Type	Criteria
A	Peripheral bile leak (there is a reconnection to the main bile duct system)
A1	Leak from the cystic duct
A2	Leak of the gallbladder bed
B	Stenosis of the main bile duct, no injury
B1	Incomplete
B2	Complete
C*	Tangential injury of the common bile duct
C1	Small punctiform lesion (< 5 mm)
C2	Extensive lesion (> 5 mm) below hepatic bifurcation
C3	Extensive lesion at the level of the hepatic bifurcation
C4	Extensive lesion above the level of the hepatic bifurcation
D	Complete transection of bile duct
D1	Without defect below the hepatic bifurcation
D2	With defect below the hepatic bifurcation
D3	At hepatic bifurcation level (with or without defect)
D4	Above the hepatic bifurcation level (with or without defect)

Type	Criteria
E	Strictures of the main bile duct
E1	Main bile duct short circular (< 5 mm)
E2	Main bile duct longitudinal (> 5 mm)
E3	Hepatic bifurcation
E4	Right main bile duct/segmental bile duct

*with vascular lesions (i.e. C1d, C2, etc.): d, right hepatic artery; s, left hepatic artery; p, proper hepatic artery; com, common hepatic artery; c, cystic artery; pv, portal vein.

Table 8. Hanover classification.

Name	Year
Bismuth classification	1982
Siewert classification	1994
McMahon classification	1995
Strasberg classification	1995
Amsterdam classification	1996
Neuhaus classification	2000
Csendes classification	2001
Stewart-Way classification	2004
Sandha classification	2004
Lau classification	2007
Hannover classification	2007
Kapoor classification	2008
Li classification	2010
Cannon classification	2011
ATOM	2013

Table 9. Classification system based on publication year.

Bismuth classification predates laparoscopic era and it defined the type of stricture based on the anatomic location with respect to the hepatic bifurcation and level at which healthy tissue is available for surgical reconstruction. Strasberg updated this classification because with advent of laparoscopic technique, injuries became more complex. (Current surgical therapy). Some classifications systems, like Hanover, implement concomitant injury of nearby vascular structures. Schematic representation of Bismuth-Strasberg and Stewart-Way classification is given in **Pictures 1** and **2**. In response of myriad of classification systems presented in literature, the European Association for Endoscopic Surgery held a consensus conference on iatrogenic bile duct injury in 2011 with a goal of devising comprehensive system to be used as the

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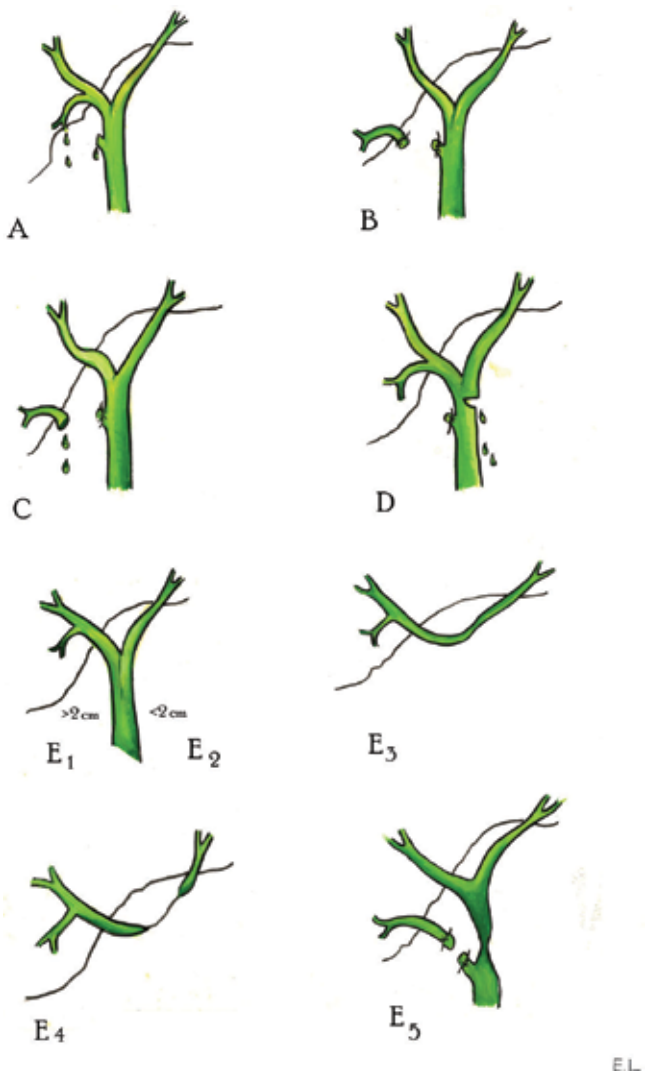
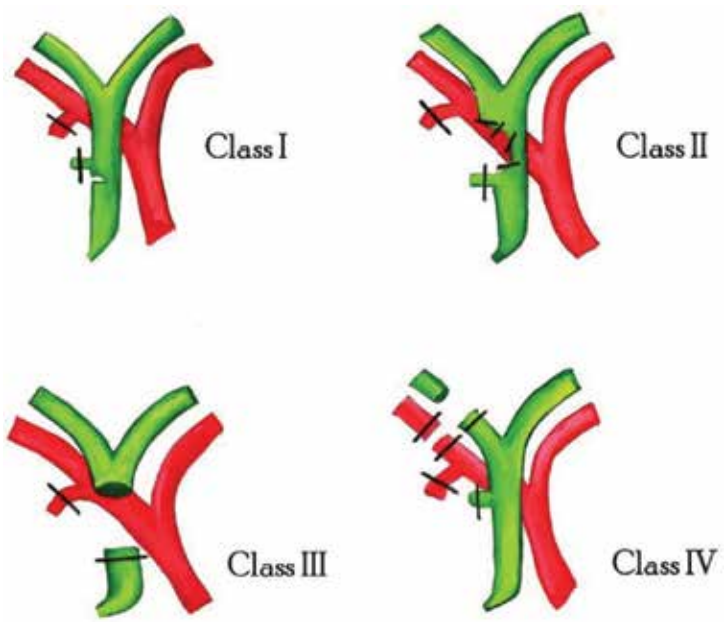


Picture 1. Bismuth-Strasberg classification of bile duct injuries. Images are attributed to Emanuela Lekić.

universally accepted classification. The result was organized into three categories: anatomic, time of injury, and mechanism (ATOM) [4].

In the future, it is important to establish universal classification system for traumatic as well as iatrogenic injuries and this classification system has to include the site of injury, the extent of injury, the type of injury and mechanism of injury so it could give the basis for establishing universal treatment options which would then be dependent on the type of the classification. This is obviously hard to accomplish since there are so many classification systems available. ATOM classification can be the right step in establishment of universally accepted classification system which then would form a basis of therapeutic options and algorithms for optimal treatment which are lacking.



Picture 2. Stewart-way classification of bile duct injuries. Images are attributed to Emanuela Lekić.

3. Etiology and mechanism of injuries

Injuries to the liver, biliary tree and pancreas are commonly referred to as the "surgical soul". They can be deadly and challenging to treat and they demand multidisciplinary approach in establishing correct diagnosis which then will provide best treatment plan, and as a result, have optimal treatment outcome.

Traumatic biliary tract injuries are rare. Intrahepatic injuries occur in association with hepatic injuries in blunt (crushing injuries, direct blow to the abdomen, falls form heights, motor vehicle accidents) or penetrating (stabbing and gunshot wounds) abdominal trauma. Incidence of bile leaks, i.e. biliary injuries in liver trauma is estimated between 4 and 23% [5]. They are suspected upon identification of bile within the peritoneal cavity. Mechanism of blunt injuries is that of acceleration/deceleration. Since liver is intraperitoneal organ which is fixed at certain points in the abdominal cavity (falciform ligament, coronary ligament, left and right triangular ligament) sudden change in movement which happens in these injuries can lead to tear, rupture or avulsion of liver parenchyma and subsequently to the injury of intrahepatic biliary tree. Mechanisam of extrahepatic biliary injuries is similar. They occur in 3 to 5% of all abdominal trauma victims, with 85% resulting from penetrating wounds. Of the remaining 15%, resulting from blunt trauma, the vast majority, 85%, involve the gallbladder alone [6]. There are very few reports in the literature of isolated extrahepatic biliary tract injuries. Some report isolated injuries of gallbladder and in literature it is said that gallbladder is the site

of injury in about 85% of cases in isolated extrahepatic biliary tract traumatic injuries. Since gallbladder is anatomically well protected it is postulated that sole injury to the gallbladder in blunt abdominal trauma occurs if the gallbladder is distended prior to injury. It is also thought that thin walled healthy gallbladders are more prone to injury than gallbladders with chronic inflammation with thick wall. Direct blows to the abdomen probable play the major role in its injury. Gallbladder is much more frequently injured in penetrating abdominal trauma. Injuries to the gallbladder can be classified as contusions, avulsions or lacerations as is mentioned in AAST classification system (**Table 2**). Almost all patients with injuries to the gallbladder have associated intra-abdominal injuries, and nearly 50% of patients are hemodynamically unstable on admission [7]. Solitary injuries of the extrahepatic bile ducts are even more rare. Only 125 such cases are found in literature in 1989 review. [8] Mechanism of injury is similar to those in gallbladder injury. Injuries can include right or left hepatic duct, common hepatic duct, cystic duct and common bile duct. Result of an injury can be partial laceration or complete transection of ducts. It is interesting to note when concerning common bile duct injuries that associated injuries to other structures in portal triad (proper hepatic artery and portal vein) does not happen as frequently as common bile duct injury. Probable explanation is that portal vein is valves and hepatic artery tortuotic hence they are less prone to shearing force unlike common bile duct which has points of fixation. Another fact that can be drawn from case reports of those injuries is that very large number of them is situated in most distal

Trauma, mostly abdominal
• blunt trauma
• penetrating trauma
Abdominal surgery
• Cholecystectomy (open or laparoscopic)
• Pancreatobiliary resection
• Biliary reconstruction
• Hepatic resections
• gastric and duodenal surgical procedures
Endoscopic procedures
• ERCP
Percutaneous procedures
• PTC
• Liver biopsy
• Stricture dilatation
• Radiofrequency tumor ablation
• Embolization

Table 10. Etiological factors in biliary injuries, traumatic and iatrogenic.

part of common bile duct, behind the head of the pancreas where common bile duct is fixed. Reports of isolated injuries of right and left hepatic duct sore extremely rare. Injuries of cystic duct should be viewed and treated as gallbladder injuries and if there is no other injury treatment after correct preoperative or intraoperative diagnosis is made, is straightforward and it consists of cholecystectomy.

Iatrogenic injuries occur mostly during laparoscopic cholecystecomy. The rate of clinically relevant bile leaks after conventional open cholecystectomy ranges between 0.1 and 0.3%. In contrast, biliary leakages have increased in the era of laparoscopic cholecystectomy by up to 3%. There are multiple factors which can cause those injuries such as inexperience of the surgeon, endoscopist or radiologist, anatomical variations in the region which are common, inflammation of gallbladder and surrounding tissue which is the most usual factor causing error, and as consequence injury to the bile duct. Injuries to the biliary tree, whether traumatic or iatrogenic manifest themselves as bile leak. **Table 10** summarizes etiological factors of injuries of biliary tract.

4. Diagnosis and presentation

Imaging modalities are very important in establishing the diagnosis, delineating the extent of injury and planning appropriate intervention. Those include cholescyntigraphy, computed tomography (CT), Ultrasonography (US), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), hepatobiliary iminodiacetic acid (HIDA scan) and fluoroscopy. Each of these techniques has different advantages and limitations and many patients undergo several imaging studies for diagnostic evaluation. Cholescintigraphy has high accuracy for the detection of bile leaks but it has poor utility in localization of the site of ductal injury. CT and US can depict fluid collections, biliary duct dilatation and associated arterial injuries. CT has higher sensitivity than US for detection of those injuries. Some authors suggest using HIDA scan before CT when bile leak is suspected since CT imaging has inadequate sensitivity for detecting biliary tract disruption [9]. MRCP provides excellent delineation of the biliary anatomy proximal and distal to the level of injury, unlike ERCP and PTC. It can give functional assessment of the biliary tract for detection and localization of bile leaks. ERCP evaluates biliary tract distal to the level of injury and is more invasive than MRCP. Advantage of ERCP is that it allows simultaneous therapeutic interventions such as the placement of biliary stents and drainage catheters which are standard for treating injuries. The main limitation of ERCP is that it does not allow evaluation of the part of the biliary tract proximal to a major duct transection or ligation and its utility is limited after surgical bilioenteric anastomosis. PTC is the method of choice when interventions such as percutaneous transhepatic biliary drainage are indicated. It is superior to ERCP for evaluation of proximal bile duct injuries, common bile duct transection or ligation and transection of the aberrant hepatic ducts.

Intrahepatic biliary injuries can be diagnosed immediately during damage control surgery which should be done for associated liver trauma in hemodynamic unstable patient. In those

patients priority is to stop hemorrhage which is done by liver packing so naturally eventual intrahepatic biliary injuries can be missed. After hemodynamic stability is achieved abdomen is closed. It is important to put a drain near liver, usually in subhepatic or subphrenic space or both. Mortality of patients is dependent on extensiveness of concomitant injuries. If the patient survives initial injury diagnosis of intrahepatic biliary injury will usually be evident by bilious content in abdominal drain placed on initial operation. This diagnosis is apparent. If there is no drainage from abdomen or abdominal drains are not places or are removed because natural course of disease, biliary injury can be missed. Clinical course can be insidious and delay in diagnosis is not uncommon. Patients usually present with unspecific systemic and local symptoms like abdominal distension, increasing pain, involuntary guarding, nausea, vomiting, elevated body temperature, icterus, acholic stools and bilirubin in urine. Similar symptoms also appear if injury is that of extrahepatic biliary system. High degree of suspicion is necessary in establishing a correct diagnosis in those cases. Treatment options depend on type, location and extent of injury. When iatrogenic injury occurs, it can be spotted intraoperatively or intraprocedura or have late presentation. Late presentation is somewhat similar to traumatic injuries. Course of treatment is largely dependent on timing of establishing the diagnosis.

5. Treatment options

Traumatic biliary tract injuries are not common so there can be a challenge and difficulty in their diagnosis. If they are recognized late and thus, managed inappropriately they can have fatal consequences. The approach to the treatment is dependant primarily on the hemodynamic status of the patient. The principles of operative management in the unstable patient follow the guidelines of damage control surgery [10]. Following blunt hepatic trauma, biliary complications have been reported in 2.8 to 7.4% of patients [11].

Depending on the type of injury, treatment of these injuries in hemodynamically stable patient can be endoscopic, percutaneous or surgical. It is important to note that percutaneous and endoscopic interventions may be performed as definitive treatment or as a adjunction to definitive surgical repair. Optimal treatment is achieved with a multidisciplinary approach. The right treatment option depends on establishment of correct diagnosis (type of injury, it's extensiveness and it's anatomical site). Also, there is an importance in timing of the diagnosis. As mentioned above some biliary tract injuries can go unnoticed and manifest themselves days, months or even years later. Main sign of biliary tract injuries is bile leakage. It can be classified as minor or major. Major biliary leaks are those draining >400 mL/day or persistent drainage >14 days [12]. Importance of this classifications lays in fact that minor bile leaks can be treated conservatively with drainage only while major bile leaks require more aggressive treatment (usually ERCP with stent placement and sphincterotomy).

Initial management of bile duct injuries focuses on stabilizing the patient's status after which bilomas should be drained and visualization of the injury with cholangiography should be

obtained. Collections which are suspected to be bilomas should be promptly drained because of the risk of development of complications such re sepsis, cholangitis or abscess formation if drainage is not done. If there is complete ligation of the ducts or their transection PTC is usually required for placement of drains which achieves biliary decompression and diversion. Complications of percutaneous biliary interventions can be classified as major or minor [13]. They are shown in **Table 11**.

Advantage of ERCP is that it is as diagnostic also a therapeutic tool. Most biliary leaks, if the injury is not complete transection of common bile duct or hepatic duct, can be treated successfully with ERCP. Treatment consists of putting biliary stent with or without sphincterotomy (there are contrary reports in literature whether sphincterotomy is necessary). The goal of the treatment is establishment of biliary decompression and biliary drainage to the upper digestive system. Stent can then be removed in following ERCP procedure. Timing of removal is also matter of controversy and most authors suggest removal of stent 3 to 8 weeks after placement. Some even suggest prolonged time for stent removal explaining that this can reduce formation of stricture formation which is usual complication of biliary tract injuries. Treatment of the injuries of the gallbladder is cholecystectomy, independent of mechanism of injury. Exception is when the first operative procedure is of damage control type. In those situations cholecystostomy can be made for biliary drainage and cholecystectomy should be done in second operation after achieving hemodynamic stability of the patient and after treatment of life threatening concomitant injuries.

Surgical therapy consists mainly on Roux-en-Y hepaticojejunostomy [14]. Available data suggests that these injuries, if surgical therapy is mandated, it should be managed by a hepatobiliary surgeon with extensive expertise in biliary reconstructions as outcomes

Major complications
• Sepsis
• Cholangitis
• Bile leakage
• Major venous and arterial hemobilia
• Hemoperitoneum and subcapsular liver hematoma
• Pleural complications (pneumothorax, hemothorax, bilous effusion)
• Death
Minor complications
• Pain
• Minor bleeding
• Bacteremia
• Transient hyperamylasemia

Table 11. Complications of Percutaneous Biliary interventions.

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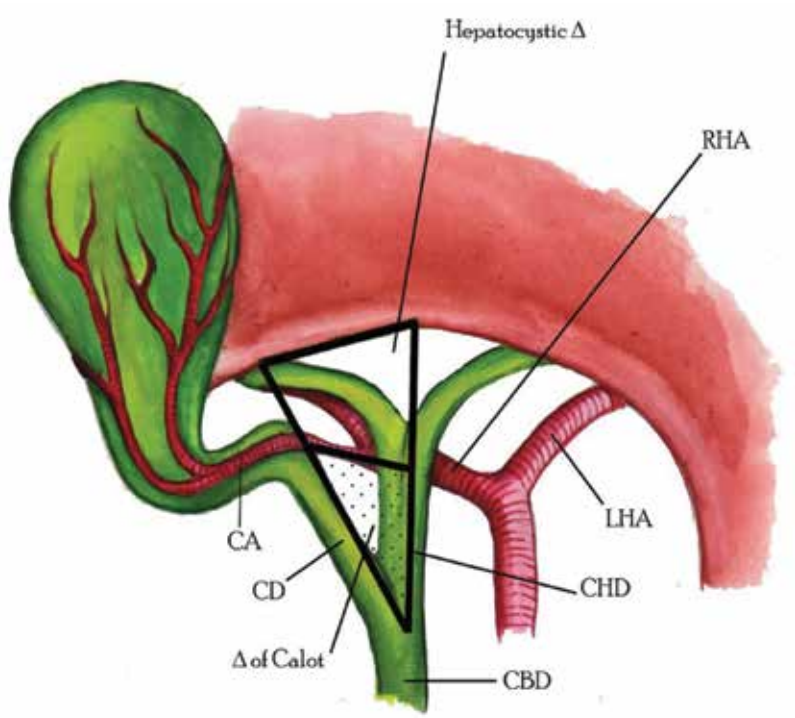
can be excellent. Because of the fact that management of these injuries often requires an experienced multidisciplinary team, they are best handled in tertiary referral center. If immediate repair is possible by an experienced surgeon, even a completely transected bile duct can be primarily reconstructed as an end-to-end ductal anastomosis by employing simple interrupted absorbable monofilament sutures. Several conditions must be met for this to succeed: the anastomosed edges should be healthy, there should be no inflammation, ischemia or fibrosis, and the anastomosis should be tension-free and properly vascularized [15]. Refreshing the proximal and distal stumps as far as the tissues are healthy and without inflammations should be performed. End-to-end ductal anastomosis can be recommended for patients when the maximal loss of length of the bile duct is 4 cm. Approximation of both ends is possible by means of a wide Kocher maneuver. The need of insertion of T-tube after such reconstruction is controversial. In the setting where a two-step approach has to be undertaken because either the injury was not identified at initial surgery or an experienced surgeon was not available, the goal of surgical repair should be the establishment of a tension-free, mucosa-to-mucosa duct enteric anastomosis, which in the majority of the cases will be an and-to-side Roux-en-Y choledochojejunostomy or, more commonly, a Roux-en-Y hepaticojejunostomy. In the cases of strictures involving the bifurcation or left or right hepatic ducts, bilateral hepaticojejunostomy may be necessary [16]. Isolated injuries to the right or left hepatic ducts could be treated by simple ligation if the primary repair is impossible or biliodigestive anastomosis is not feasible because of hemodynamic instability of the patient [17]. Nonoperative management of bile duct injury, if there are no complete transections of bile duct, is effective with success rate ranging from 90 to 94% [18]. In summary, the key to successful treatment of iatrogenic bile duct injuries is early recognition, control of intraabdominal bile ascites and inflammation, nutritional repletion, and repair by a surgeon with expertise in biliary reconstruction. If these requirements are met, patients can have successful repair with long-term success in more than 90% of cases [19]. Traumatic biliary injury is a rare but important consequence of abdominal trauma, and good outcomes are possible when a major trauma center and hepatopancreaticobiliary service is present. Cholecystectomy is the gold standard for treatment of gallbladder injuries. Drainage with or without stenting will resolve majority of intrahepatic and partial biliary injuries. Hepaticojejunostomy is the gold standard for complete extrahepatic biliary disruption [20]. Regardless of the type of biliary injuries management, wide drainage is essential [21].

6. Prevention of iatrogenic biliary tract injuries

Cholecystectomy is one of the most frequent surgeries done in the world. Since the rise of laparoscopy most of these procedures are done laparoscopically. The consequence of laparoscopic cholecystectomy is increase in the incidence of iatrogenic injuries to the extrahepatic biliary tract. This is the reason why it is important to establish measures to decrease the incidence of these injuries. There are many proposals in literature how to accomplish

that, form education in laparoscopy to anatomical landmarks which can guide the surgeon during procedure and changing the surgical technique itself. There is great emphasis on identifying the structures in, so called, Calot triangle [22], and hepatocystic triangle, **Picture** 3, which is bordered by liver surface, common hepatic duct and cystic duct. It should be always identified during laparoscopic cholecystectomy. Misidentification of the bile ducts is the leading cause of biliary injury. To avoid this, the "critical view of safety" technique should be employed with utmost care. Inexperienced surgeons should be cautious about using the single-incision technique, as this may increase the risk of biliary injury in difficult cases. If biliary injury is identified intraoperatively, reconstruction should only be undertaken by experienced hepatobiliary surgeons. In the postoperative period, any deviation from the expected clinical course of recovery should alert the surgeon to suspect biliary injury and take a proactive approach to diagnosis and proper management [23].

In order to decrease the chance of biliary injury a group of authors formed Delphi consensus [24] which outlined factors and proposed actions during surgical procedure in order to minimize and decrease the incidence of iatrogenic lesions. Those are summarized in **Table 12**.



Picture 3. Hepatocystic triangle and triangle of Calot. Images are attributed to Emanuela Lekić.

When to stop

- Extensive and dense adhesion to surrounding organs and/or greater momentum
- Impacted gallstone in the confluence of the cystic, common hepatic, and common bile duct (included in the expanded classification of Mirizzi syndrome)
- Severe fibrosis and scarring in Calot's triangle due to inflammation
- Severe fibrosis and scarring in gallbladder bed due to inflammation (includes sclero-atrophic gallbladder)
- Anomalous bile duct
- Extensive operative time
- Extensive blood loss

Where to stop

- Rouviere's sulcus
- Sentinel lymph node (cystic lymph node of Lund)
- Base of segment IV (hilar plate)
- Calot's triangle area
- Infundibulum-cystic duct junction (so-called elephant trunk sign)
- Sclero-atrophic gallbladder (so-called hump sign)
- Critical view of safety
- SS inner layer

How to prevent

- Decompression of a distended gallbladder with needle aspiration
- Effective retraction of the gallbladder to develop a plane in the Calot's triangle area and identify its boundaries (countertraction)
- Starting dissection from the posterior leaf of the peritoneum covering the neck of the gallbladder and exposing the SS inner layer above Rouviere's sulcus
- Maintaining the plane of dissection within the SS layer (i.e. exposing the SS inner layer) throughout laparoscopic cholecystectomy
- Dissection the lower part of the gallbladder bed (at least one-third) to obtain the critical view of safety
- Always obtaining the critical view of safety
- For persistent hemorrhage, achieving hemostasis primarily by compression and avoiding extensive use of electrocautery or clipping
- Intraoperative cholangiography
- Intraoperative ultrasound
- Intraoperative indocyanine green fluorescent imaging

What are the alternatives

- Open conversion
- Fundu-first (dome-down)
- Subtotal (partial) cholecystectomy
- Cholecystectomy (drainage only)

Table 12. Summarized key results in Delphy consensus on avoidance of biliary duct injuries.

7. Postoperative management and complications

Patients with injuries of biliary tract, after successful initial management can have complications which can be serious in nature. Most common complication following the management of these injuries is development of biliary stenosis if the primary repair was done for incomplete rupture of ducts and after removal of previously placed stent or complication can be in the formation of chronic biliary fistula. Strictures can also develop after hepaticojejunostomy. Cholangitis is also frequently described complication. These complications must be discussed with the patient and the patient must be informed of possible occurrence of symptoms of these complications (jaundice, abdominal pain, fever, malaise, nausea, vomiting) before discharge after management of initial trauma and injury. Chronic strictures can be managed by dilatation with either an endoscopic or percutaneous approach [25]. Surgical approach, revision and repair may be needed in patients with unsuccessful endoscopic or percutaneous treatment. Biliary fistulas may develop if primary repair was incomplete, if there is prolonged external drainage through T tube or drain site and if the injuries are missed. For fistulas that do not close, surgical intervention by an experienced biliary surgeon may be required. Postoperative follow up is not required. Repeated imaging diagnostic (CT, ERCP or other) should be based on patient's symptoms and laboratory findings. Recent data shows that there is no significant difference in health related quality of life in long-term follow up after successful repair of biliary tract injuries [26].

8. Conclusion

Biliary tract injuries, whether they are traumatic or iatrogenic, are rare and literature coverage of the subject is scarce in reporting traumatic injuries. Intrahepatic biliary injuries are always associated with liver trauma. Acute treatment options are focused on achieving hemodynamic stability if the patient is unstable due to hemorrhage form liver trauma so missed initial diagnosis of intrahepatic biliary injuries is not uncommon. Those patients usually have abdominal drains places and diagnosis of such injury is suspected by contents of abdominal secretion from drain. Delayed diagnosis of intrahepatic biliary injuries is very frequent, mainly because symptoms are unspecific and with gradual onset. High index of suspicion is necessary for that diagnosis. Patients usually present with nausea, vomiting, icterus, acholic stools and with bile in urine. Abdominal distension and gradual increase in involuntary guarding and muscle rigidity is common. Treatment plan is molded depending on correct diagnostics. It is important to identify a site of biliary leakage and it's dynamic and, based on those information's, plan treatment options accordingly. Main complications of intrahepatic biliary tract injuries are hemobilia and biloma formation. In most cases simple drainage (preferably percutaneous) is suffice. Natural history of bile duct injuries is spontaneous closure within 3 weeks if the biliary drainage is maintained. Conservative management of those injuries is safe option if the abdominal cavity is drained and remains afebrile.

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Extrahepatic biliary tract trauma as a solitary entity is extremely rare. Injuries of the extrahepatic biliary tree are usually accompanied with injuries to the adjacent organs, i.e., liver, duodenum, pancreas. Solitary extrahepatic biliary traumatic injury is reported mostly as case reports and selected reviews of those reports in literature. It is usually result of a blunt abdominal trauma. As with intrahepatic lesions which are missed during initial patient workup because of concomitant trauma, extrahepatic biliary injuries are often missed. After initial shock from trauma recovery ensues and after initial quiet period symptoms usually arises third to tenth post injury day. They are similar as those described above in intrahepatic injuries since the pathophysiological mechanism behind symptomatology is the same. It is important to emphasize the achievement of correct diagnosis since the treatment options, which can be more or less aggressive (surgical, endoscopic, percutaneous) larger if not solely are dependent on establishing the correct diagnosis, meaning correct site of injury, extent of injury and associated injuries. Treatment options are ERCP with stent placement with or without sphincterotomy, percutaneous transhepatic biliary drainage, transabdominal biliary drainage or surgical approaches which usually consist of Roux n Y bilioenteric anastomosis or primary repair. All treatment options have the same goal: decompression of bile flow and establishment of biliary drainage into digestive system.

Iatrogenic biliary tract injuries are consequence of surgical, endoscopic or percutaneous techniques on biliary tract or adjacent organs. There is an increase in incidence of those injuries with advent of laparoscopic procedures comparing to open surgery. Vast majority of those injuries are consequence of laparoscopic cholecystecomy. Most important aspect of those injuries is early (intraoperative, intraprocedural) recognition. Delayed presentation resembles the injuries of traumatic nature with late recognition. Management plans is largely dependent on type of injury and correct diagnosis. Most widely used technique is hepaticojejunal Roux-en-Y anastomosis. Prevention of iatrogenic injuries is important and literature reports numerous recommendations to avoid such injuries during procedures. One of the most important is Delphi consensus.

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Biliary mucincous cystic neoplasms

Chapter 6

Mucinous Cystic Neoplasms of the Liver and Extrahepatic Biliary Tract

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Additional information is available at the end of the chapter

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Abstract

Mucinous cystic neoplasms of the liver and extrahepatic biliary tree have recently been re-defined by WHO as epithelial cystic tumours with ovarian-type mesenchymal stroma. Correct recognition of these tumours can be difficult because of their rarity and, consequently, lack of awareness by the medical team. Radiological evaluation, including ultrasonography, computed tomography, magnetic resonance imaging and, upon necessity, positron emission tomography, can yield the correct diagnosis. Radical surgical resection with tumour-free margins is the mainstay of treatment. Adequate treatment approach can be very rewarding, bringing prolonged survival. Here we discuss the up-to-date concepts of definition and classification, theoretical views on tumour origin along with practical issues of clinical presentation, diagnostics, treatment and prognosis.

Keywords: mucinous cystic neoplasm, liver, liver tumour, biliary cystadenoma, biliary cystadenocarcinoma

1. Introduction

Mucinous cystic neoplasms of the liver [1], formerly known as bile duct/biliary cystadenoma and biliary cystadenocarcinoma [2], represent an enigmatic entity, characterised by unknown origin and peculiar morphology including the presence of ovarian-type stroma. Clinically, these tumours are important albeit rare. Mucinous cystic neoplasms of the liver can be diagnostically challenging because of several reasons, including (1) prolonged clinical course suggesting a benign disease or even harmless liver cyst; (2) controversial radiologic presentation;

and (3) insufficient experience of the involved medical team. Consequently, it might be difficult to select the best treatment. Lack of awareness of these unusual tumours is an important cause of diagnostic and surgical mistakes. To enhance the knowledge of medical society on the mucinous cystic neoplasms of the liver, here we aim to summarise contemporary data on these tumours, including the current definition and classification [1], the recent molecular genetic findings [3, 4] as well as the practical issues of clinical presentation, diagnostic approach, treatment and prognosis.

2. Definition and evolution of the concept

Currently, mucinous cystic neoplasms of the liver are defined as epithelial cystic tumours associated with ovarian-type mesenchymal stroma. They are further subclassified by (1) presence or absence of invasion and (2) in non-invasive tumours—by the highest grade of epithelial atypia [1]. Thus, four entities are obtained (**Table 1**). Although intrahepatic location predominates, mucinous cystic neoplasms with true ovarian-type stroma can primarily develop in extrahepatic biliary ways [5, 6] or show extrahepatic extension [7].

The previous classification by WHO (2000) included bile duct cystadenoma/cystadenocarcinoma, defined as cystic tumours, that were lined by mucus-secreting or, less frequently, serous epithelium [2]. Stroma was not set as a diagnostic criterion.

Considering the current WHO definition [1] in the context of preceding classifications and morphology, three aspects must be kept in mind.

2.1. Diagnostic importance of the ovarian-type stroma

Mucinous cystic neoplasms of the liver were formerly referred to as bile duct/biliary cystadenoma and cystadenocarcinoma. However, the presence of ovarian-type stroma was not mandatory in the preceding entities. It was present in the mucinous type of benign cystadenomas, but was absent from the serous type of biliary cystadenomas [2] as well as from a subfraction of cystadenocarcinomas [8]. In contrast, currently only tumours with ovarian-type subepithelial stroma are classified as mucinous cystic neoplasms [1]. The cases lacking the specific stroma could represent intraductal papillary neoplasms of bile ducts with marked

Biologic potential	Diagnosis	ICD-O code
Non-invasive mucinous cystic neoplasms of the liver	Mucinous cystic neoplasm with low-grade intraepithelial neoplasia	8470/0
	Mucinous cystic neoplasm with intermediate-grade intraepithelial neoplasia	8470/0
	Mucinous cystic neoplasm with high-grade intraepithelial neoplasia	8470/2
Mucinous cystic neoplasms of the liver with an invasive component	Mucinous cystic neoplasm with an associated invasive carcinoma	8470/3

Table 1. Classification of the mucinous cystic neoplasms of the liver [1].

cystic changes [1]. The rearrangement of classification is in accordance with the previously well-known observation that biliary cystadenocarcinoma without ovarian-type stroma has distinctly worse prognosis [8–10] (it must be noted that contrary and neutral reports also have been published: see [11, 12], respectively) and is more frequently observed in males [8, 11].

2.2. Extent of mucus secretion

The neoplastic epithelium in fact may lack mucus production [1, 4]. Still, neoplasms showing ovarian-type stroma are not classified as serous cystadenomas [1].

2.3. Criteria to identify malignant cases

In the current classification, invasive and non-invasive tumours are clearly separated. In contrast, the preceding diagnostic criteria of biliary cystadenocarcinoma included invasion, cellular atypia, and mitotic activity to recognise a malignancy. Although invasion was underlined as the hallmark of malignant course, presence of cell atypia and mitoses also justified the diagnosis of carcinoma [2]. Currently, non-invasive cases showing anaplastic cell morphology would be classified as mucinous cystic neoplasms with high-grade intraepithelial neoplasia [1].

Unfortunately, terminological controversies and disagreements still remain. Although the current WHO classification redefined mucinous cystic neoplasms already on 2010, the preceding terms of biliary cystadenoma and cystadenocarcinoma are still in use [5, 13–15]. Ovarian-type stroma has been neglected as a diagnostic criterion, e.g., in a recent (2015) multicentric study only 33.3% of the evaluated biliary cystic tumours actually had this feature [11]. Some research teams have expressed disagreement with the present classification [5]. There are repeated discussions on cases lacking both ovarian-type stroma and communication with biliary ducts—a separate entity has been hypothesised [16].

3. Epidemiology

Mucinous cystic neoplasms of the liver are rare tumours. Previously, incidence of biliary cystadenoma was estimated to range between 1:20,000 and 1:100,000, while incidence of biliary cystadenocarcinoma was reported to be 1:10 million [10]. Considering, that cases of biliary cystadenocarcinoma without ovarian-type stroma are reclassified as intraductal papillary neoplasms and non-invasive tumours showing cell anaplasia—as mucinous cystic neoplasms with high-grade intraepithelial neoplasia, the true incidence of malignant mucinous cystic neoplasms of the liver is even lower. The incidence of benign tumours also might change in accordance to the current (2010) WHO classification. Non-invasive mucinous cystic neoplasms of the liver that were previously diagnosed a biliary cystadenocarcinomas on the basis of cell atypia and mitotic activity, would be transferred to the benign group, increasing it, albeit slightly [1, 2]. On the contrary, the rare [10] serous type of biliary cystadenoma, defined by the previous WHO classification (2000), was known to lack ovarian-type stroma and nowadays would be excluded from the group of mucinous cystic neoplasms of the liver [1, 2]. Considering the whole group of mucinous cystic neoplasms with ovarian-type stroma, 25% of cases that were previously diagnosed as hepatobiliary cystadenoma/cystadenocarcinoma were reclassified as other entities according to the current WHO classification [15].

Feature	Mucinous cystic neoplasms of the liver[1]		Biliary cystic tumours[2]	
	Non-invasive	Invasive	Cystadenoma	Cystadenocarcinoma
Gender: proportion of female patients	Almost all [1]	Unclear proportion [1]	84.2% [22]	0% [22]
			96% [8]	33.3% [23]
			100% [15, 23, 24]	56% [8]
				71.4% [24]
				100% [15]
Mean age, years	45 [1]	59 [1]	40.6; range, 30–51 [24]	51.3; range, 41–63 [24]
			45; range, 2–87 [8]	59; range, 24–90 [8]

[1]According to WHO Classification of Tumours of the Digestive System, 2010 [25].

[2]According to World Health Organisation Classification of Tumours: Pathology and Genetics of Tumours of the Digestive System, 2000 [26].

Table 2. Demographic characteristics of mucinous cystic neoplasms of the liver.

Geographic differences have been highlighted by Zen et al. [17]. Comparing the numbers of intraductal papillary neoplasm of bile ducts and mucinous cystic neoplasm of the liver in medical institutions of Seoul, Seattle and London, the ratios were 5.7:1; 1:3.0 and 1:6.3, respectively. In Eastern countries, intraductal papillary neoplasms are significantly more frequent [17].

In a recent large study, mucinous cystic neoplasms with ovarian-type stroma accounted for 11% of resected cystic liver lesions in a single institution [15]. However, this proportion should not be applied to all liver cysts found by radiologic investigation as only a small fraction of liver cysts needs surgical treatment [9, 18, 19]. Even the frequently cited assessment that mucinous cystic neoplasms constitute 5% of cystic liver lesions [13, 19, 20] is known to be an overestimate [18] otherwise the incidence of biliary mucinous cystic tumours would exceed the occurrence of cholangiocarcinoma which is not observed. Instead, mucinous cystic neoplasms might represent 5% of symptomatic liver cysts referred for surgical treatment. In 1996–1997, biliary cystadenocarcinoma accounted for 0.18% of all liver tumours registered by Japanese Liver Cancer Study Group [9]. However, it has been noted that mucinous cystic neoplasms are rare in Japan [21]. Currently, invasive mucinous cystic neoplasms constitute 0.41% of hepatic carcinomas [19].

Although the demographic characteristics of the patients vary slightly depending on the classifications (**Table 2**), there are some essential general trends, including a strong female preponderance, predominant occurrence in middle-aged people and earlier age of diagnostics in benign/non-invasive cases.

4. Tumour origin and tissue structure

The presence of ovarian-type mesenchymal stroma raises questions on the origin of mucinous cystic neoplasms of the liver. The correct hypothesis should explain both the presence of this unusual feature and the structural similarity with mucinous cystic tumours of the pancreatic

gland and retroperitoneal space showing similar stroma [27]. During embryogenesis, ectopic ovarian rests might develop in the liver, along biliary tree, in the pancreas or retroperitoneal tissues and stimulate the proliferation of adjacent biliary or pancreatic ducts by synthesis of growth factors [9, 28]. Indeed, during embryonic development, gonads initially are located directly under the diaphragm, dorsally to the liver and pancreatic tail, and only later they descend to the typical anatomic location seen in adults. The local morphologic appearance of embryonic peritoneal lining with swollen, activated-looking cells is also suspected to be an evidence of interaction between gonadal primordia and developing liver/pancreas, situated just across peritoneal cavity [29].

Origin from intrahepatic peribiliary glands has been preferred by some authors, based on morphological similarity, presence of endocrine cells both in mucinous cystic tumours and in peribiliary glands, and a huge autopsy investigation on 938 livers [1, 30]. In the given autopsy study reported by Sato et al., cystic and micropapillary changes in peribiliary glands were sought for and subjected to morphological and immunohistochemical analysis. Cystic glands were found in 4% of the examined livers while micropapillary lesions were present in 1%, but showed association with an invasive adenocarcinoma in a single case. Micropapillary areas exhibited marked mucus secretion, up-regulation of cyclin D1 and higher proliferative fraction by Ki-67, suggesting that these cell groups possessed a premalignant potential [30].

The peribiliary origin of mucinous cystic neoplasms of the liver seems to be the preferable explanation for the parallels with analogous pancreatic tumours. Biliary tract along with peribiliary glands has considerable structural similarity with pancreatic ducts and acini. Indeed, the biliary tree has even been designated as "incomplete pancreas". The structural similarity is reflected in several pathologies (**Table 3**), not limited to mucinous cystic neoplasms [27]. The peribiliary glands could also eventually receive stimulation by ectopic ovarian stroma—thus, both the aforementioned theories fuse together.

However, not all scientists support the hypothesis of ectopic ovarian tissues. Although the morphology of the specific mesenchymal component closely resembles ovarian stroma, there is also a remarkable similarity to embryonal tissues that are destined to form gallbladder or foregut [10]. The stromal immunophenotype is largerly unspecific, characteristic for myofibroblasts. Hormone receptor expression, including both oestrogen and progesterone receptors, has been found in human embryonic stem cells [33] as well as in abdominal fibromatosis [34], not only in the stroma of ovaries. Thus, according to Ockham's razor, simpler explanation might include origin from peribiliary glands influenced by embryonal-like fibroblasts. Such view allows considering not only congenital but also acquired origin as proposed by Cruickshank and Sparshott [35], possibly a response to a focal injury or oestrogen-containing oral contraceptives [10, 18]. Indeed, a significant fraction of patients has history of obesity, heavy alcohol use, or hormone-related therapy [36].

Research team of D'Errico found that biliary cystadenocarcinomas co-expressed high levels of biliary cytokeratins (by immunohistochemistry) and albumin mRNA (by *in situ* hybridisation). This might indicate either tumour origin from pluripotent stem cells or re-acquisition of embryonal features. *In situ* hybridisation for albumin mRNA was proposed to distinguish between cystadenomas and cystadenocarcinomas; the association with malignancy might rather indicate dedifferentiation and not an evidence of the origin of biliary mucinous cystic neoplasms [37].

Pathogenesis and characteristics	Biliary diseases	Pancreatic diseases
Pre-invasive flat intraepithelial neoplasia, representing a precursor of a solid invasive tumour	**Biliary intraepithelial neoplasm: the precursor of nodular sclerosing cholangiocarcinoma**	**Pancreatic intraepithelial neoplasm: the precursor of pancreatic ductal adenocarcinoma**
Grossly visible, mass forming, primarily intraductal neoplasms that can lead to duct obstruction with papillary tumour masses and secondary cystic dilation of obstructed ducts, followed by intracystic tumour growth. Invasive component can develop	**Intraductal papillary neoplasm of bile ducts**	**Intraductal papillary mucinous neoplasm of pancreas**
Presence of gross cysts	Frequent, secondary to duct dilation	Frequent, secondary to duct dilation
Involvement and dilation of ducts	Frequent	Frequent
Mucus secretion	Frequent	Frequent
Ovarian-type stroma	Absent	Absent
Prognosis	Can progress to an aggressive invasive cancer	Can progress to an aggressive invasive cancer
Patients	Males and females	Males and females
Mucinous cystic neoplasms: cystic tumours with subepithelial ovarian-type stroma	**Hepatobiliary mucinous cystic neoplasm**	**Pancreatic mucinous cystic neoplasm**
Presence of gross cysts	Always	Always
Involvement and dilation of ducts	Rare or absent	Rare or absent
Mucus secretion	Frequent but variable	Frequent but variable
Ovarian-type stroma	Always	Always
Prognosis	Good after complete surgical resection	Good after complete surgical resection
Patients	Mostly: middle-aged females	Mostly: middle-aged females
IgG4-related autoimmune inflammation with mass (pseudotumour) development	**IgG4-inflammatory pseudotumour**	**Mass-forming type 1 autoimmune pancreatitis**

Table 3. Biliary diseases with pancreatic counterparts [9, 27, 31, 32].

5. Morphology: from gross findings to the molecular landscape

5.1. Gross structure

Grossly, the tumours represent a single cyst or a multilocular cystic lesion: a dense group of several cysts recognised by the cyst-in-cyst appearance or the presence of internal septations [1, 21]. Multilocular structure (see **Figure 1**) predominates, in contrast to (1) simple cysts lacking internal septations and (2) intraductal papillary neoplasms exhibiting multicystic appearance: a grape-like cluster of adjacent cysts [21]. Thus, among 20 mucinous cystic neoplasms of the liver and extrahepatic bile ducts, there were 2 unilocular and 18 multilocular neoplasms [5].

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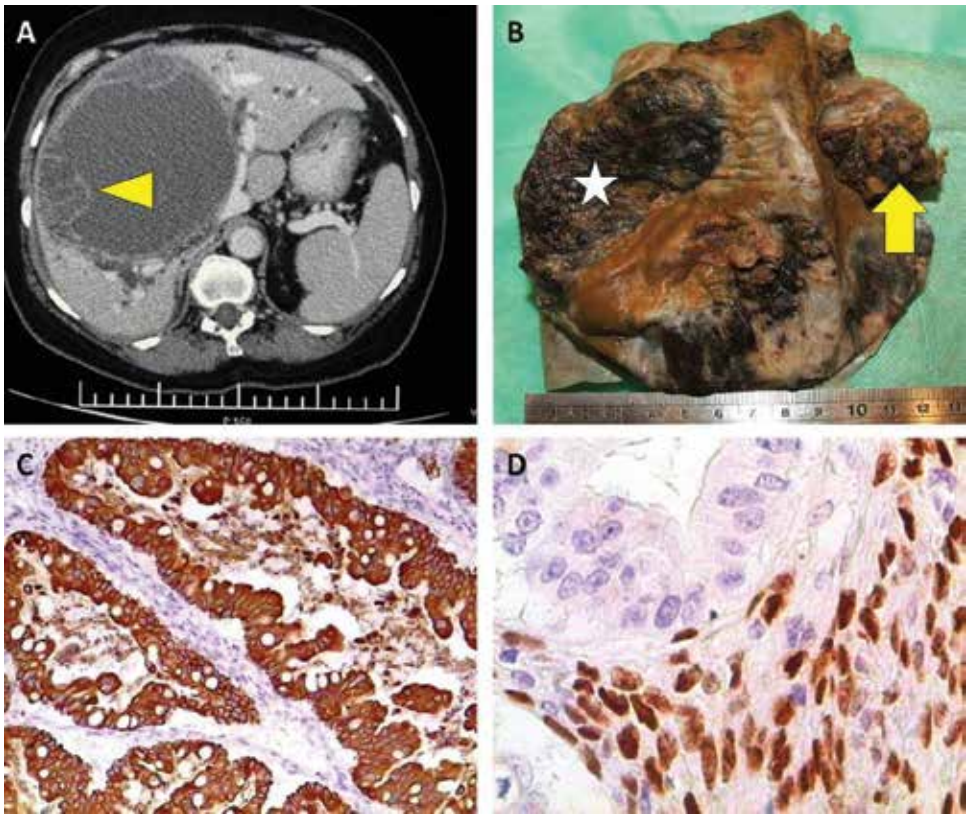

Figure 1. Mucinous cystic tumour of the liver. A, computed tomography findings. Note the huge cyst with internal septations (arrowhead). B, gross view. Note the nodule (arrow) harbouring invasive malignancy. Widespread haemorrhage (star) also is present. C, intense expression of cytokeratin 20 in an area of intestinal differentiation, showing rich presence of goblet cells. Immunoperoxidase (IP), original magnification (OM) 100×. D. Intense nuclear expression of progesterone receptors in the ovarian-type stroma. Note the absence of reactivity in the epithelium. IP, OM 400×.

The frequency of multilocular tumours is estimated to be 84%. In non-invasive cases, fibrous capsule delineates the whole tumour. Even invasive tumours mostly show only a limited spread within the fibrous pseudocapsule [38]. Extrahepatic development is less frequently seen, e.g., in a series of 20 cases, only 4 patients had an extrahepatic tumour [5]. The frequency of extrahepatic mucinous cystic neoplasms of biliary tree has been variably estimated to range between 3 and 20% [5, 39], averaging 10% of all mucinous cystic neoplasms of liver [13].

The cysts usually contain clear fluid, but occasionally thick mucus or haemorrhagic content can be found [1]. The tumour size is variable, reported to range from 1.2 to 40 cm in diameter [38]. A grossly evident communication with larger bile ducts is not typical. If present, such feature may suggest the diagnosis of an intraductal papillary neoplasm of bile ducts [31]. Papillary areas and mural nodules (**Figure 1**) should be identified grossly, described in the surgical pathology report and sampled extensively as these foci are suspicious for malignant change [1]. In contrast, trabeculation of the inner surface can be seen even in cystadenomas [10].

5.2. Microscopic characteristics of epithelium

Histologically, the cysts are lined by epithelium. The height and cytoplasmic structure of epithelial cells varies widely: from cylindrical to flat, from mucus secreting to cases in which only a small amount of mucus can be highlighted by mucicarmine stain or tumours with serous appearance of epithelium [1]. Typical epithelium is cuboidal, columnar or tall, with pale eosinophilic cytoplasm and basally located nuclei [10]. Mucus secretion is not marked in significant fraction of the considered tumours albeit the entity is designated as mucinous cystic neoplasms of the liver [4]. For instance, among 20 cases of mucinous cystic tumours of the liver and extrahepatic bile ducts, 18 tumours were predominantly composed of cuboidal or low columnar epithelium that was similar to the lining of bile ducts. Only two cases showed rich mucus secretion along with intestinal differentiation and presence of goblet cells [5]. Among 36 mucinous cystic neoplasms of the liver and extrahepatic biliary tree, non-mucinous epithelium was predominant in 50% cases [15]. Gastric, intestinal (**Figure 1**) or squamous differentiation can also occur. Basement membrane is present in non-invasive cases [1].

Enlarged, hyperchromatic, crowded nuclei, loss of nuclear polarity and presence of mitoses indicate intraepithelial neoplasia. High-grade intraepithelial neoplasia is characterised by glandular crowding, significant nuclear pleomorphism and brisk mitotic activity. The architectural disarray in high-grade intraepithelial neoplasia manifests both as papillary elevations and crypt-like invaginations into the stroma. The latter must be distinguished from true invasive growth.

Invasion is the hallmark of malignancy and must be acknowledged in the diagnosis as a mucinous cystic neoplasm with an associated invasive carcinoma [1]. The frequency of invasive carcinoma in mucinous cystic neoplasms of the liver or extrahepatic biliary ways has been variably reported to be 2 [17]; 6 [15]; 10 [4] or 15.4% [40]. In some series, invasion was not found, e.g., there were no invasive carcinomas among 29 mucinous cystic neoplasms described by Zen et al., although a single case of so-called carcinoma *in situ* was identified [21]. In contrast, the proportion of malignant cases by the preceding WHO classification (2000) was as high as 38.5% [41]. If present, invasive areas tend to be small, e.g., in the only 2 (of 36 investigated mucinous cystic neoplasms of the liver or extrahepatic biliary tree) invasive cases, the invasive areas measured merely 7–8 mm [15].

5.3. Molecular features in correlation with morphology

The amount of cytoplasmic mucus is an interesting and significant feature of neoplastic epithelium (**Table 4**). As mentioned, in a significant fraction of cystic tumours, mucinous epithelium is not the dominant type: it occupies less than 50% of surface and can be as limited as 10%. Nevertheless, such cases are still diagnosed as mucinous cystic neoplasms of the liver if ovarian-type stroma is present. Although the terminology might seem slightly confusing, sufficient experience of pathologist will easily allow overcoming the diagnostic problems. However, there is a far more important aspect: the degree of mucinous differentiation is shown to parallel the frequency of *KRAS* mutations and of invasive carcinoma [4]. Already earlier, intestinal metaplasia with the presence of goblet cells (**Figure 1**) has been acknowledged as a premalignant lesion [10].

Reference	Parameter	Total number	Mucinous differentiation	
			Marked	Weak
Shibata et al. [4]	Study group	15 mucinous cystic neoplasms of liver (2) and pancreas (13)	6	9
	KRAS mutation	6	5	1
	Invasive carcinoma	2	2	0
Albores-Saavedra et al. [42]	Study group	31 mucinous cystic neoplasms of pancreas	22	9
	Invasive carcinoma	6	6	0
Zhelnin et al. [43]	Study group	136 mucinous cystic neoplasms of liver (32) and pancreas (104)	71	58
	High-grade intra-epithelial neoplasia	8	8	0
	Invasive carcinoma	14	14	0
Albores-Saavedra et al. [5]	Study group	20 mucinous cystic neoplasms of liver (16) and extrahepatic bile ducts (4)	2[1]	18
	High-grade intra-epithelial neoplasia and invasive carcinoma	2	2	0

[1] Along with intestinal differentiation.

Table 4. Clinical and pathogenetic significance of mucinous differentiation in cystic neoplasms with ovarian-type stroma.

Thus, in a study group of 15 mucinous cystic neoplasms of the pancreas and liver, there were 6 cases with marked mucus secretion while in the remaining 9 cases less than 50% of epithelium showed obvious mucus in the cytoplasm. Invasive carcinoma was found in two cases, both from mucus-rich group. A single case of high-grade intraepithelial neoplasia also was found within the mucus-rich group. The tumours with limited amount of mucus featured only low-grade intraepithelial neoplasia [4]. Analogous findings have been reported also by Albores-Saavedra et al. [42] and Zhelnin et al. [43]. The first of these studies was devoted to pancreatic mucinous cystic neoplasms—the counterpart of hepatic tumours. Among the evaluated 31 cases, 22 showed abundant mucus production and 6 of them were associated with invasive carcinoma. In contrast, there was no invasive component in any of the nine cases presenting with non-mucinous cuboidal or low columnar epithelium [42]. Subsequently, in a large cohort comprising 136 pancreatic and hepatic mucinous cystic neoplasms, high-grade intraepithelial neoplasia (8 tumours) or invasive carcinoma (14 patients) were found only among cases with marked mucus secretion (defined as presence of microscopically visible mucus in more than 50% of neoplastic epithelial cells). There were also 58 cases with predominantly (>50%) non-mucinous epithelium, and no evidence of high-grade intraepithelial neoplasia or invasion was found among them. Both these differences were statistically significant as shown by $p = 0.007$ for high grade intraepithelial neoplasia and $p < 0.001$ for invasive carcinoma [43].

The significance of mucinous differentiation was further clarified by molecular studies. *KRAS* mutations have recently been associated with marked mucinous differentiation and malignant transformation [4]. Among 15 mucinous cystic neoplasms of the liver or pancreas, *KRAS* mutations were present in 6 cases, and 5 of them featured marked mucus secretion. Thus, the frequency of *KRAS* mutations in mucinous *versus* non-mucinous tumours was 83 *versus* 11%; p = 0.011. The mutations were found in both invasive cancers (2) and 4 cases of low-grade intraepithelial neoplasia [4]. *KRAS* mutations are confirmed to be the driver mutations in the mucinous cystic neoplasms of the liver and pancreas [3]. These genetic changes are uncommon in low-grade intraepithelial neoplasia (1/20; 5%) while are present in most of cases with invasion, intermediate- or high-grade intraepithelial neoplasia (4/5; 80%; p = 0.002). Interestingly, in *KRAS*-mutated cases that were diagnosed as intermediate- or high-grade intraepithelial neoplasia, identical mutations were found in adjacent areas of low-grade intraepithelial neoplasia. Thus, it seems that *KRAS* mutations precede and possibly drive the morphological changes. In comparison with wild-type tumours, *KRAS* mutated cases more frequently express mucins: MUC1 (pancreatobiliary), MUC2 (intestinal) and MUC5AC (gastric), as reflected by the corresponding p values: p = 0.04; p = 0.016; p = 0.015. By sequencing, no alterations of *GNAS*, *RNF43* and *PIK3CA* have been found in hepatic and pancreatic mucinous cystic neoplasms [3]. C-met activation is another pathogenetic event in the mucinous cystic neoplasms of the liver [44].

Thus, there is a considerable body of evidence that mucinous epithelium is prone to develop high-grade dysplasia and progress to invasive carcinoma. *KRAS* mutations are likely to be a significant driving force within this pathway. Still, different conclusions could follow. Albores-Saavedra proposed to reclassify cystic tumours with ovarian type stroma, separating non-mucinous cystadenomas with pancreatobiliary phenotype and ovarian-like stroma in a new entity that hypothetically had no malignant potential [42]. In contrast, Zhelnin et al. viewed the mucinous differentiation as a dynamic change: a sign of tumour progression towards malignancy [43]. The observation that non-mucinous tumours are smaller [43] and found in younger patients [4, 43] is in accordance with this assumption. Consequently, evidence of marked mucinous differentiation, e.g., by *in vivo* confocal laser endomicroscopy could prompt surgery.

5.4. Immunophenotype of epithelium

Considering the immunophenotype of epithelium, expression of cytokeratins 7, 8, 18 and 19 is characteristic in accordance with the biliary differentiation [1, 5]. As was noted, *KRAS* mutated cases more frequently expressed pancreatobiliary (MUC1), intestinal (MUC2) and gastric (MUC5AC) mucins [3]. Previously, expression of MUC1 [5] was known, and presence of cytokeratin 20, CDX2 and MUC2 was reported in association with intestinal differentiation characterised by presence of goblet cells, columnar absorptive cells and Paneth cells. Notably, cases with clear-cut intestinal differentiation frequently show invasion [42, 45]. Proliferation fraction by Ki-67 is low in benign cases but increases in the areas of malignant change [45]. Epithelial membrane antigen EMA is present [8]. Carcinoembryonic antigen CEA is focally expressed in the neoplastic epithelium [8] and thus can be found also in the cyst fluid [46]. Chromogranin-positive endocrine cells are present both in benign and malignant tumours [1, 8].

5.5. Ovarian-type stroma

The morphologic appearance of stroma is among the crucial diagnostic criteria of mucinous cystic neoplasms. The specific stroma consists of densely growing spindled cells that closely resemble ovarian tissues. No cellular atypia or mitotic activity is present in contrast with biphasic malignant tumours, e.g., carcinosarcoma or mesothelioma. Sarcomatous stromal transformation has been reported in mucinous cystic tumours of the liver and pancreas but is distinctly rare [10, 47].

The immunophenotype of stromal cells discloses mesenchymal (vimentin), and myogenic (actin and desmin) differentiation along with hormone dependence reflected by expression of oestrogen (77% of cystadenomas) and progesterone (100% of cystadenomas) receptors [1, 36]. In addition, biliary cystadenomas (13 cases) displayed uniform nuclear reactivity for FOXL2, a transcription factor that was expressed in female gonads from the early stages of development to normal adult ovarian stroma [36]. Alpha-inhibin also is found [1, 44]. The landscape of oestrogen and progesterone receptor expression (**Figure 1**) along with alpha-inhibin, calretinin and CD10 can be useful in the rare but demanding cases when differential diagnosis is between endometriosis and mucinous cystic tumours [48]. Not only the mere presence, but location of positive reaction (epithelium *versus* stroma) is of utmost importance (**Table 5**).

Three additional morphologic events, occasionally seen in stroma of mucinous cystic neoplasms, include luteinisation of stromal cells [1], calcification [10] and xanthogranulomatous reaction. The latter features cholesterol crystals (seen in tissue sections as clefts) as well as foam cells and lipofuscin-containing macrophages. The outer layer of tumour wall is represented by loose fibrous tissue [1].

Some authors have emphasised the difficulties in stromal assessment, namely, the focal nature of the specific ovarian-type tissues and inter-observer variability [11]. Among 36 mucinous cystic neoplasms of the liver and extrahepatic biliary tree, only 47% of cases demonstrated diffuse ovarian-type stroma; the diffuse spread was defined as involving >75% of cyst perimeter [15]. To overcome such problems, wide sampling and increased awareness of pathologist about mucinous cystic neoplasms will be helpful. In doubt, immunohistochemical visualisation of oestrogen and progesterone receptors in the stroma can be advised. This finding is not

Antigen	Endometriosis in the liver	Mucinous cystic tumour of the liver
Oestrogen receptors	+ stroma//+ epithelium	+ stroma//− epithelium
Progesterone receptors	+ stroma//+ epithelium	+ stroma//− epithelium
Alpha-inhibin	− stroma	+ stroma
CD10	+ stroma	− stroma
Cytokeratin 7	+ epithelium	+ epithelium
Cytokeratin 19	+ epithelium	+ epithelium

Abbreviations and symbols in the table: +, positive reaction; −, negative reaction; CD; cluster of differentiation.

Table 5. Immunophenotype of mucinous cystic tumours of the liver *versus* endometriosis [1, 48].

entirely specific; endometriosis, in particular, represents another oestrogen- and progesterone receptor positive lesion. However, it is useful for the differential diagnosis with simple cyst or intraductal papillary neoplasms, both lacking stromal hormone receptor expression.

5.6. FNA, core biopsy and frozen section: findings and limitations

The efficacy of preoperative morphological diagnostics is limited, regarding both core biopsy and fine needle aspiration (FNA) for cytology. By FNA, groups of cuboidal or columnar epithelial cells can be observed against either watery or mucinous background. The cellular atypia can be variable, depending on the degree of intraepithelial neoplasia and reflecting the heterogeneity seen within a single mucinous cystic neoplasm of the liver. As the stromal cells usually are not seen in the sample, differential diagnostics with intraductal papillary neoplasm is not reliable. FNA of intraductal papillary neoplasms yields papillae with fibrovascular cores; although papillary groups can be seen in mucinous cystic neoplasms, they are abundant in intraductal papillary neoplasms. Presence of nuclear grooves is also characteristic of intraductal papillary neoplasms. In addition to problems in distinguishing between different cystic liver lesions, the focality of sampling can decrease sensitivity of FNA for the diagnosis of malignancy [1].

Core biopsy is not advised as the cystic nature of lesions precludes obtaining of a representative tissue sample. In addition, the heterogeneity represents a further obstacle as the foci of invasive growth can easily be missed. Rarely, biopsy can lead to peritoneal carcinomatosis therefore it has been advised to avoid biopsy if surgical treatment is planned [10].

For intraoperative diagnostics, the use of frozen section is controversial. The reports range from positive experience [49] to high rate (66.6%) of false negative conclusions [40]. Intraoperative scrape cytology has been informative in at least one case, revealing both biliary epithelial and mesenchymal stromal cells [50].

6. Tumour spread and staging

As was noted, malignant biliary mucinous cystic tumours usually are characterised by limited growth, invading the fibrous pseudocapsule [38]. Only in rare cases, the tumour widely infiltrates the adjacent liver, spreads to regional lymph nodes (mainly in hepatoduodenal ligament) or distant organs, such as lungs, pleura or peritoneum [1]. TNM staging is analogous to intrahepatic cholangiocarcinoma (**Table 6**).

Parameter	Definition
T—extent of local tumour spread	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary liver tumour
Tis	Carcinoma *in situ*
T1	Solitary invasive tumour lacking vascular invasion
T2a	Solitary tumour invading blood vessels

Parameter	Definition
T2b	Multiple tumours
T3	Tumour perforates visceral peritoneum or directly invades extrahepatic tissues and organs
T4	Periductal growth pattern
N—regional lymph node status in regard to metastases	
Nx	Regional lymph node status cannot be assessed
N0	No metastases in regional lymph nodes
N1	Metastasis in regional lymph nodes has been identified
M—presence or absence of distant metastases	
M0	Distant metastasis absent
M1	Distant metastasis present
Stage	
I	Stage (I) corresponds to T value (T1) in the absence of metastases in regional lymph nodes and distant locations: T1 N0 M0
II	Stage (II) corresponds to T value (T2) in the absence of metastases in regional lymph nodes and distant locations: T2 N0 M0
III	Stage (III) corresponds to T value (T3) in the absence of metastases in regional lymph nodes and distant locations: T3 N0 M0
IVA	Either highly advanced local tumour (T4) or presence of metastases in regional lymph nodes (N1) in the absence of distant metastases: T4 N0 M0 or T1–4 N1 M0
IVB	Presence of distant metastases: T1–4 N0–1 M1

Table 6. TNM staging of mucinous cystic neoplasms of the liver [25].

7. Clinical presentation and course

The symptoms and objective findings (**Table 7**) are non-specific, attributable mainly to the presence of slowly growing mass. The clinical course is characterised by insidious onset and slow progress, consistent with the gradual advancement of the tumours (but see further for exceptions). The mass can distend liver capsule, rupture, bleed, or compress stomach or duodenum [10]. Damage of biliary tree or blood vessels is possible via compression or invasion. Consequently, benign or malignant tumours can present similarly.

Abdominal pain or discomfort [10] is the most frequent complaint [22]. Pain has been reported in 74% (range in different studies: 60–80%) of patients diagnosed with biliary cystic tumours while abdominal distention is observed in 26% and nausea/vomiting in 11% [18]. Approximately 60% of patients complain about pain in right upper abdominal quadrant or epigastric area, in combination with increasing abdominal circumference or awareness of abdominal mass. The growing tumour can also lead to vague abdominal discomfort [10].

Clinical symptoms and signs				
Dominant	**Biliary**	**Vascular**	**Other**	**Absent**
60–74%	35%	Rare	Rare	30–58%
Abdominal pain Abdominal discomfort Abdominal distension Mass (objectively)	Obstructive jaundice Skin itching Biliary colic Cholangitis Steatorrhea	Portal hypertension Ascites Compression/obstruction of the inferior caval vein	Gastric/duodenal compression Tumour rupture Bleeding Peritoneal carcinomatosis Metastatic spread	Incidental finding during unrelated radiologic or surgical exploration

Table 7. The clinical manifestations of mucinous cystic neoplasms of the liver.

Bile duct compression [10] or invasion can lead to obstructive jaundice and predispose to ascending infection resulting in cholangitis. If the tumour contents are discharged into bile ducts, mucobilia is possible. Bleeding to biliary ways results in haemobilia [51]. Biliary symptoms are seen in 35% of patients with benign tumours referred to as cystadenomas by WHO classification, 2000 [10] and can be responsible for acute presentation or intermittent course, in addition to the more classical slowly progressing clinical picture.

Biliary obstruction (caused by the tumour itself, mucobilia with thick mucus or haemobilia with clots) may present as obstructive jaundice, skin itching, biliary colic, cholangitis, nausea, fever or steatorrhea. Intermitted course with repeated bouts of jaundice, biliary colic or cholangitis has been reported [10]. Notably, obstructive jaundice can be caused by benign tumour as biliary cystadenomas with ovarian-type stroma can show expansive growth with prolapse into bile duct. The prolapse is seen by endoscopic retrograde cholangiopancreatography as an oval-shaped filling defect in the bile duct. To exclude a stone, endoscopic ultrasonography and intraductal ultrasonography are useful, since multiple septa are found in tumours. At least 17 such cases have been reported in the medical literature, 2004–2015 [52].

Haemobilia denotes bleeding towards the bile ducts. In general, most cases of haemobilia are caused by trauma or iatrogenic injury from percutaneous biliary tract instrumentation. Haemobilia as a primary presentation of liver tumour is unusual. In a systematic review of 222 cases of haemobilia over 3-year period, only 14 cases were caused by tumours. Nevertheless, Philip et al. have reported a male patient presenting with anaemia (haemoglobin 6.7 g/dL) and recurrent haemobilia confirmed during duodenal endoscopy. Repeated CT and MRI scans initially could not identify liver mass. During re-bleeding episode, the mass was found radiologically, but its histogenesis remained unclear until postoperative histology [51].

Gastric or duodenal compression may present as slowly progressing upper gastrointestinal obstruction with nausea, vomiting, dyspepsia and/or anorexia [10].

Among unusual manifestations, compression of portal vein can lead to portal hypertension and ascites in the absence of cirrhosis. Compression/obstruction of the inferior caval vein with subsequent bilateral leg oedema has been reported [38].

In addition, the patients can be asymptomatic. Although it has been noted that mucinous cystic neoplasms of the liver "nearly always cause symptoms at the time of presentation" [1], this might merely reflect the cases in which diagnosis is reached at the point when patients insist on solving the diagnostic enigma after several years of controversial findings. Indeed, occasionally the patients have as long clinical history as 10 years [53]. The symptoms are likely to be size-dependant; thus, small mucinous cystic neoplasm of the liver can present as an incidental finding. Clinically silent presentation is reported in up to 42.1% of cases [22] and is expected to become more frequent with increasing availability of medical services. Indeed, the frequency of asymptomatic presentation has been noted to range between 30 and 58% [38]. The asymptomatic tumours might be revealed as an accidental finding during radiological investigation or abdominal surgery for other clinical indications [10].

At least a fraction of patients experiences lengthy diagnostics and relapse after insufficient treatment. Thus, Thomas et al., noted that the symptoms lasted in average for 3.1 years; and eight of their patients (8/19) had had 20 procedures prior to definitive ablation [18].

8. Radiological findings and differential diagnosis

Cystic neoplasms of the liver are rare while simple liver cysts are common, seen in 2.5–18% of population [54]. Radiological investigation is the mainstay of preoperative diagnostics in order to discriminate between simple liver cyst and mucinous cystic neoplasm. Estimates of the biological potential (benign *versus* malignant) and differential diagnostics with other cystic lesions, e.g., parasites, abscesses or cystic/necrotic metastases, represent other important tasks [28].

The essential methods of liver evaluation include transabdominal ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI). Positron emission tomography (PET) can be helpful in detecting malignancy. Mucinous cystic neoplasms of the liver, as the term emphasises, are cystic and usually large masses (although small tumours have been reported). To distinguish these tumours from simple liver cysts, presence and vascularity of internal septa are important. Some authors have found that vascularity of the septations is more specific than the mere presence of septa, if the differential diagnosis between a simple cyst and a mucinous cystic neoplasm of the liver is carried out [18, 24]. Other research teams emphasised the importance of finding internal septa that started perpendicularly to the outer wall and were not associated with external indentation [55]. CT can better disclose the enhanced internal septations even if they are thin; the cyst content is usually hypoattenuating [56]. By contrast-enhanced ultrasound (CEUS) imaging, biliary cystic tumours mostly (78.3%) display honeycomb enhancement pattern of the cyst wall, septa or mural nodules [14]. Prolonged enhancement in Kupffer phase is not characteristic but occasionally can be caused by rich presence of macrophages [57]. On MRI, mucinous cystic tumours are hypoattenuating on T1W1; however, high protein content in cyst fluid might increase the signal intensity. On T2W1, the fluid is hyperintense, and septations are better visible [56]. In addition, mucinous cystic neoplasms more frequently are solitary if compared with simple liver cysts [58]. Synchronous cases represent an unusual exception [59].

In turn, presence of enhanced mural or septal nodules is the most important sign of malignancy [38]. In contrast, benign cystic tumours have smooth and thin walls and internal septa. Calcification in the mural nodules is a controversial finding—some but not all [24, 60, 61] authors associate it with malignant tumour (in the context of mucinous cystic neoplasms of the liver). By CEUS, benign tumours are characterised by hyperenhancement of the honeycombed septa during arterial phase ($p = 0.047$) while malignant cases feature significantly ($p = 0.041$) more frequent hypoenhancement during the portal venous and late phases [14]. The experience with PET is very limited, but the reported data reflect correct identification of malignant process [18, 38].

Simple cysts are asymptomatic, single or multiple lesions with thin wall and watery contents. Thus, in CT or MRI simple cysts are seen as non-enhancing, well circumscribed, fluid-containing foci [38]. Multiple cysts can be present in patients affected by autosomal dominant polycystic liver disease, and these cases are more prone to haemorrhage. MRI can be helpful to identify it thus solving the differential diagnosis. The autosomal recessive Caroli disease represents another inherited liver disease associated with cyst development. In Caroli disease, cavernous ectasias of bile ducts develop, frequently associated with stone formation. Radiologically, communications between the cystic cavities and biliary duct system are important. "Central dot" sign is observed by CT. Bridges across the cavities are evident by MRI. Both these findings represent branches of portal vein embedded in connective tissue strands adjacent to and surrounded by dilated bile ducts [28].

Embryonal sarcoma, a rare and usually solid malignant tumour of adolescence, occasionally has cyst-like appearance on CT and MRI because of myxoid stroma. Both the age and the presence of wide solid component are helpful to exclude mucinous cystic neoplasm of the liver [28].

Other malignant tumours, especially metastases, occasionally have cyst-like appearance because of necrosis or accumulation of mucus. Necrotic metastases are seen in CT or MRI as foci with strong peripheral enhancement and irregular border; usually there are multiple lesions. Mucinous metastases most frequently represent metastatic colorectal or ovarian carcinoma. In the latter case, the characteristic transperitoneal spread by implantation can lead to development of multiple nodules within the liver capsule while mucinous cystic neoplasms of the liver are located within liver parenchyma. Neo-adjuvant treatment sometimes induces cyst-like degeneration of metastases [62]. On rare occasions, other malignant tumours develop unusual cystic appearance, e.g., angiosarcoma [63], Ewing sarcoma [64], primary or metastatic neuroendocrine neoplasm [62, 65] or hepatocellular carcinoma [66].

Multiple cystic liver lesions are seen in echinococcosis, characterised by multi-layered wall of the cysts and presence of multiple small hypoattenuating daughter cysts with thin eggshell calcifications. Serologic tests will confirm the diagnosis [28].

Liver abscess initially is seen as a cluster of small foci that later converge into an unilocular cystic lesion. It might contain gas formed by microbial flora. Later, thick, enhancing wall develops. "Double target" sign can be evident because of peripheral rim enhancement attributable to increased capillary permeability. However, invasive growth of malignant tumours

can incite similar inflammatory response. Presence of mobile debris seen by US is characteristic of abscess [28].

History of trauma or operation is helpful to suspect a bile collection (biloma) or hematoma. Biloma is visible in CT and MRI as a well-demarcated cystic focus lacking septa, calcifications or pseudocapsule [28].

9. Assessment of cyst fluid

Regarding the analysis of cyst fluid, the diagnostic value is controversial. Promising reports have suggested that high concentrations of certain proteins in the cyst fluid might help to distinguish cystic tumours from simple cysts thus aiding in case selection for surgery. Assessment of cyst fluid would be free of problems related to sampling of heterogeneous tissues—a frequent problem in obtaining and interpretation of biopsy. Elevated levels of carbohydrate antigen CA19-9, significantly exceeding the concentration of CA19-9 in the serum, have been reported in cyst fluid [22]. Increased concentrations of CEA and CA19-9 in the cyst fluid are described in cystic tumours but not in simple liver cysts [46]. However, comparing the levels of CA19-9, CEA and cancer antigen 125, no significant differences ($p = 0.45$; $p = 0.49$ and $p = 0.73$, respectively) were found between 13 mucinous cystic neoplasms and 38 simple hepatic cysts [58]. Still, in a larger group including 32 mucinous cystic tumours and 40 simple cysts, a significantly elevated CA19-9 level in tumours was shown. The differences were demonstrated both by the median level of CA19-9 (364.8 *versus* 21.4 U/mL) and the fraction of cases in which CA19-9 exceeded the highest value of laboratory reference interval for serum assessment (46.9 *versus* 10.0%). The concentrations of CEA lacked significant difference; the median value was 6.8 mg/L in tumours *versus* 4.2 mg/L in simple cysts [67]. Tumour-associated glycoprotein (TAG) 72 has been suggested as a highly informative marker for differential diagnosis between mucinous cystic tumours and simple liver cysts. Performing ROC curve analysis, TAG-72 concentration exceeding 25 U/mL was associated with specificity and sensitivity of 0.97 and 0.79, respectively, being superior to CEA and CA19-9 and yielding area under curve (AUC) of 0.98 for the discrimination between cystic tumours and simple cysts [68].

Regarding pancreatic counterparts, attractive future research directions have appeared regarding diagnostics by cyst fluid assessment, e.g., next generation sequencing for driver mutations (e.g., *KRAS*) in the cyst content [69], combined evaluation of CEA and *KRAS* status [70]; or CEA, CA19-9, cytological and ultrasonographic findings [71]. Elaboration of combined diagnostic algorithms based on several features, including detection of tumour markers, viscosity [72], mucinous differentiation [73], *KRAS* testing, proteome analysis [74] in the cyst fluid and ultrasound or CT features, is pathogenetically substantiated, up-to-date [75] and promising direction. However, any preoperative cyst sampling involves low but not negligible risk of complications, including peritoneal or pleural dissemination, or pseudomyxoma in malignant cases [20]. In addition, the differential diagnostic background in pancreas also differs from liver—an organ, affected by simple cysts in up to 18% of the general population [54].

10. Treatment

Once the diagnosis of a mucinous cystic liver neoplasm has been established, surgery is the mainstay of the treatment. These tumours have two essential biological features: (1) capacity to recur after incomplete excision and (2) slow progression towards malignant transformation, seen with reasonable frequency [10]. Therefore complete surgical resection is strongly advised. The intent must be to remove all the neoplastic tissues. However, considering the low biological potential of these neoplasms, wide resection margin is not mandatory. Thus, enucleation or liver resection (hepatectomy, bisegmentectomy and extended hepatectomy) represent appropriate approaches while marsupialisation, internal Roux-en-Y drainage, aspiration, sclerosing or partial resection are associated with high rate of complications, mainly recurrence or sepsis [18, 20, 28]. Enucleation with clear margins is the preferable option for large central tumours, associated with/located close to blood vessels or large bile ducts [20]. Liver transplantation has been suggested in unresectable cases including recurrent or giant tumours [61, 76].

The recurrence rate after an incomplete resection is as high as 90% therefore an undiagnosed mucinous cystic liver neoplasm should be suspected in any patient who experiences a relapse after treatment of presumed simple liver cyst, e.g., marsupialisation (deroofing) or partial resection [20]. Although such recurrences bring the risk of malignant change, the biological potential of mucinous cystic tumours is low and recurrent patients still are amenable to surgery, even after repeated relapses and over as long time period as 10 years [18, 20, 53].

There is very limited experience with treatment other than surgery. Argon beam plasma coagulation has occasionally been used as an adjunct to surgery. A case of biliary cystadenocarcinoma has been reported in which the main focus was removed by non-anatomic liver resection while a satellite lesion underwent fulguration. The patient experienced prolonged survival and was free of disease 2142 days (5.9 years) after operation [18].

The data on the efficacy of primary or adjuvant chemo-/radiotherapy are limited to few case reports. For instance, systemic, 5-fluoruracil-based chemotherapy was reported effective in a single patient who had recurrence and multiple metastases of biliary cystadenocarcinoma 41 months after surgical removal. The patient benefitted from tumour reduction and clinical improvement [28]. In another patient, major hepatectomy was not amenable because of insufficient functional reserve of the liver, but hepatic arterial infusion of cisplatin helped to reduce the size of the tumour from 12 cm in diameter to 2 cm and to improve the general condition [77]. Three patients have received chemo-radiotherapy as a primary treatment. The 2-year and 5-year survival was 33.3% [39]. Currently, the reported experience with chemotherapy is clearly insufficient.

11. Prognosis

Exact prognostic data are difficult to obtain because of two problems: (1) rarity of mucinous cystic tumours leading to predominantly small study groups and (2) contamination of even

these cohorts with cases lacking ovarian-type stroma. As shown further, as least a fraction of tumours lacking the specific stroma might represent intraductal papillary neoplasms that are associated with worse outcome. However, general lines still can be drawn.

The prognosis depends both on the presence or absence of invasion [78] and metastatic spread (albeit rare) as well as on the completeness of resection. After complete removal of a benign tumour, the prognosis is excellent. The overall survival is 90% over 18 years [13]. Zen et al. reported on 24 surgically treated cases; all patients were alive during follow-up of 1–132 months; median 47 months [21]. Some authors have not experienced recurrence of a benign cystic mucinous tumour after appropriate surgical treatment while others note the risk of recurrence ranging between 5 and 13% [13, 21]. Incomplete surgical removal leads to recurrence [18, 21]. In untreated cases or in patients subjected to non-radical approach, malignant change can develop; the risk is estimated to be as high as 20% [13].

Although malignant tumours can recur after surgery, the prognosis of surgically removed invasive mucinous cystic tumour of the liver is significantly better than for other primary malignant liver tumours, including hepatocellular carcinoma or cholangiocarcinoma. Prolonged survival can be expected. Even disease-free survival after radical resection of cystadenocarcinoma was 16.5 and 33 months [22]. The 5-year survival of surgically resected malignant mucinous cystic tumour of the liver is 65–70%, contrasting with 40% in hepatocellular carcinoma and 22% in cholangiocarcinoma [13]. If relapse develops, mostly it is local, but some patients (up to 20%) experience extrahepatic metastases [13].

Mucinous cystic tumours of the liver are associated with better prognosis than intraductal papillary tumours. After resection of mucinous cystic neoplasm of the liver, 5-year survival rate was 100%, contrasting with 84% in patients diagnosed with intraductal papillary neoplasm of bile duct [79]. Similarly, the 5-year survival of surgically treated hepatic mucinous cystic neoplasms (13) including malignant cases (38.5%) was 100%, exceeding the outcome of intraductal papillary neoplasms: 5-year survival rate in this group was 82% [41].

12. Conclusions

Mucinous cystic neoplasms of the liver, formerly known as biliary cystadenoma and cystadenocarcinoma in accordance with WHO classification (2000), have been redefined by WHO (2010) as epithelial cystic neoplasms with ovarian-like stroma. They are subclassified by the presence or absence of invasion. Non-invasive cases are further distinguished by the highest grade of intraepithelial neoplasia.

Although the exact incidence has to be clarified in subsequent studies, mucinous cystic neoplasms of the liver are rare. Previously, the incidence of biliary cystadenoma was estimated to range between 1:20,000 and 1:100,000, while the incidence of biliary cystadenocarcinoma was reported to be 1:10 million. Considering the whole group of hepatic and biliary mucinous cystic neoplasms with ovarian-type stroma, 25% of cases that were previously diagnosed as

biliary cystadenoma/cystadenocarcinoma might be reclassified as other entities according to the current WHO classification.

The origin of these tumours is unclear. The best substantiated hypotheses point towards peribiliary origin, possibly in association with ectopic ovarian stroma or remnants of embryonal gall bladder or foregut tissues. The most important advances in morphologic and molecular studies include mucinous differentiation as a progression phenomenon, indicating development towards malignancy and identification of *KRAS* mutations as the molecular driver force.

The clinical presentation is unspecific. Mass effects are dominant, leading to abdominal pain or discomfort. Biliary obstruction can be seen both in benign and malignant cases, being caused by expansive growth and prolapse into biliary ways or by invasion, respectively. Biliary symptoms are observed in 35% of patients and include obstructive jaundice, skin itching, biliary colic, cholangitis, mucobilia, haemobilia, nausea, fever or steatorrhea. Bile duct involvement can be responsible for acute presentation or intermittent course, in addition to the more classical slowly progressing clinical picture.

Radiological evaluation is the mainstay of diagnostics, as both FNA and core biopsy have limited informativity. The essential methods of liver evaluation include transabdominal ultrasonography, computed tomography, magnetic resonance imaging and positron emission tomography. Mucinous cystic neoplasms of the liver are cystic, usually large and solitary. To distinguish these tumours from simple liver cysts, presence and vascularity of internal septa are important. In turn, presence of enhanced mural or septal nodules is the most important sign of malignancy. Calcification in the mural nodules can indicate malignancy, but is controversial. The experience with PET is very limited, but the reported data reflect correct identification of malignant process.

In turn, radical surgery is the main treatment option. The intent is to remove all the neoplastic tissues. However, considering the low biological potential of these neoplasms, wide resection margin is not mandatory. Thus, enucleation or liver resection represent appropriate approaches while marsupialisation, internal Roux-en-Y drainage aspiration, sclerosing or partial resection are associated with high rate of complications, mainly recurrence or sepsis. After complete resection of non-invasive tumours, the prognosis is excellent. Prolonged survival can be expected even in invasive cases.

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Conflict of interest

The authors have no conflict of interest to declare.

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The basic researches and clinical studies on biliary tree diseases continue to advance at a rapid pace. The articles in this book were written by recognized medical experts and researchers from North America, Europe, Asia, and Africa and aim to provide state-of-the-art reviews on the current knowledge and advances in the surgery of the biliary tree. It includes the most recent advances in that field, particularly cholangiocarcinoma, biliary tree injuries, and biliary cysts.

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