We are IntechOpen, the world's leading publisher of Open Access books
Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 2

Intrahepatic Cholangiocarcinoma

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

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.75516

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

IntechOpen

© 2018 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

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].

http://dx.doi.org/10.5772/intechopen.75516

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

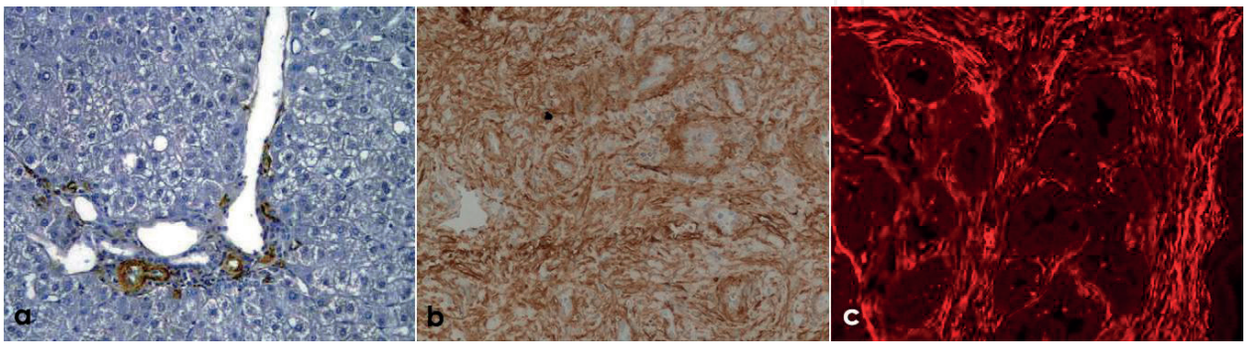

Figure 1. Alpha-SMA expression in normal liver parenchyma (in brown, a) and in cholangiocarcinoma specimen at immunohistochemistry (b) and at immunofluorescence (in red, c), personal series.

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

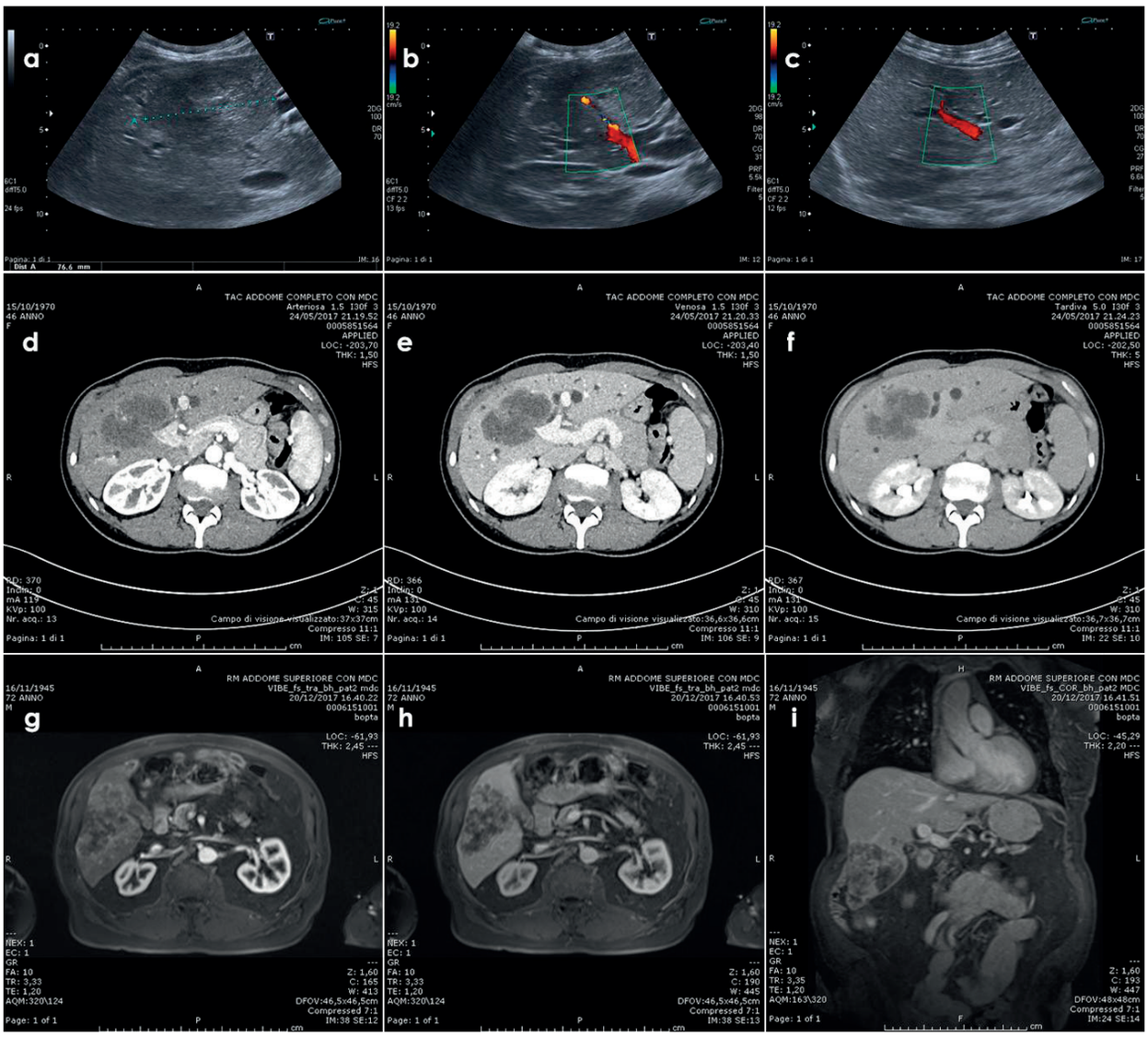

Figure 2. Mass-forming intrahepatic cholangiocarcinoma. (a–c) Abdominal ultrasound confirming the dilatation of intrahepatic biliary ducts, locating the site of obstruction. It appears as a homogeneous, hypoechoic lesion. (d–f) CT scan, the lesion is hypoenhanced, with capsular retraction and biliary 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

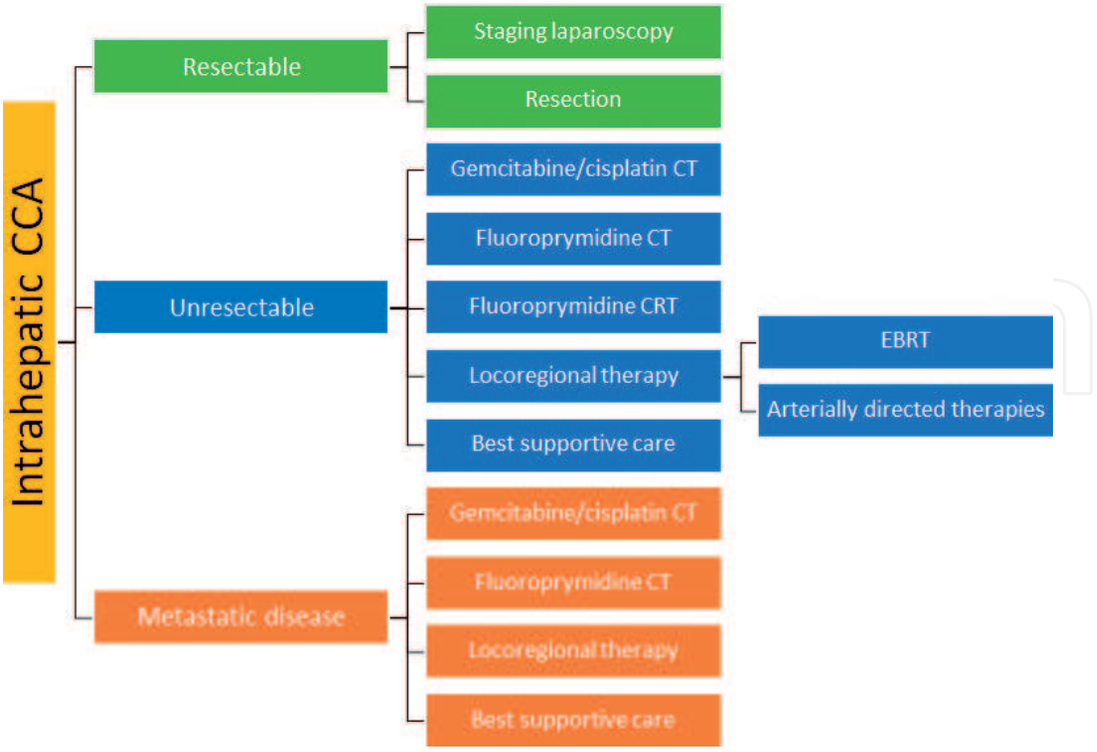

Figure 3. Treatment flowchart.

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)

http://dx.doi.org/10.5772/intechopen.75516

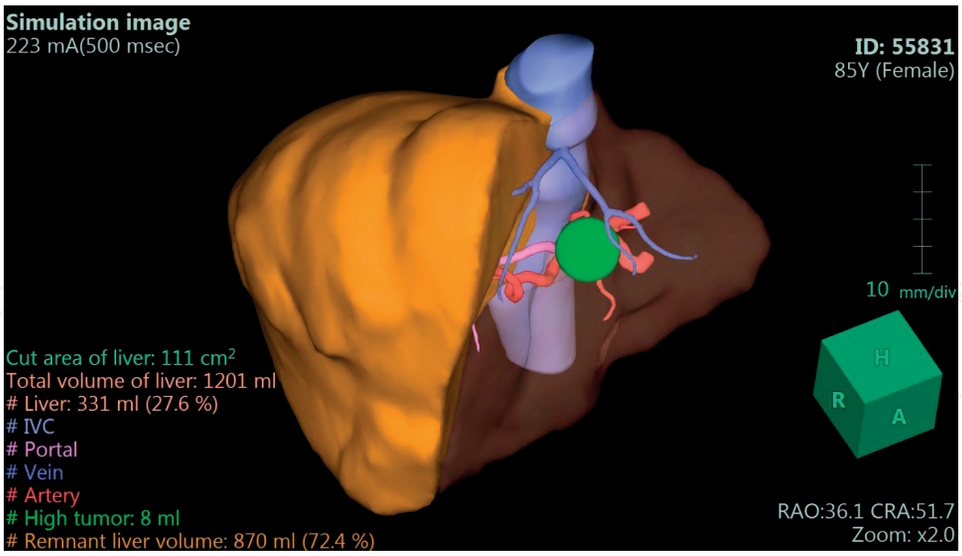

Figure 4. Volumetric liver analysis. It is performed to determine total liver volume (TLV) and future remnant liver volume (FRLV) and remnant liver volume percentage (RLV%).

[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

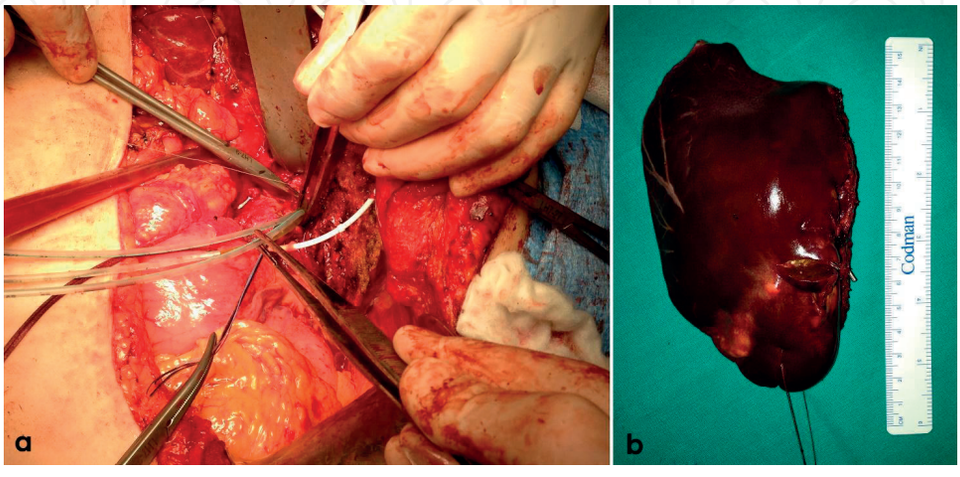

Figure 5. Intrahepatic CCA. (a) Left hepatectomy, biliary resection, and bilioenteric anastomosis with right anterior bile duct S5/8, right posterior bile duct S6/7, and segmental S1 bile duct and (b) left lateral sectionectomy.

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.

Author details

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

*Address all correspondence to: marco.massani@aulss2.veneto.it

IV Department of Surgery, Regional Center for HPB Surgery, Treviso Regional Hospital, Treviso, Italy

References

[1] Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology. 2013;**145**:1215-1229. DOI: 10.1053/j.gastro.2013.10.013

[2] Banales JM, Cardinale V, Carpino G, Marzioni M, Andersen JB, et al. Expert consensus document: Cholangiocarcinoma: Current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). Nature Reviews. Gastroenterology & Hepatology. 2016;**13**:261-280. DOI: 10.1038/nrgastro.2016.51

[3] Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD. Cholangiocarcinoma. Lancet. 2005 Oct 8;**366**(9493):1303-1314. DOI: 10.1016/S0140-6736(05)67530-7

[4] Aljiffry M, Walsh MJ, Molinari M. Advances in diagnosis, treatment and palliation of cholangiocarcinoma: 1990-2009. World Journal of Gastroenterology. 2009;**15**:4240-4262. DOI: 10.3748/wjg.15.4240

[5] Nakeeb A, Pitt HA, Sohn TA, Coleman JA, Abrams RA, et al. Cholangiocarcinoma: A spectrum of intrahepatic, perihilar, and distal tumors. Annals of Surgery. 1996;**224**:463-475. DOI: 10.1097/00000658-199610000-00005

[6] Ebata T, Kosuge T, Hirano S, Unno M, Yamamoto M, et al. Proposal to modify the International Union Against Cancer staging system for perihilar cholangiocarcinomas. The British Journal of Surgery. 2014;**101**:79-88. DOI: 10.1002/bjs.9379

[7] Welzel TM, Mellemkjaer L, Gloria G, Sakoda LC, Hsing AW, et al. Risk factors for intrahepatic cholangiocarcinoma in a low-risk population: A nationwide case-control study. International Journal of Cancer. 2007;**120**:638-641. DOI: 10.1002/ijc.22283

[8] Alvaro D, Bragazzi MC, Benedetti A, Fabris L, Fava G, et al. Cholangiocarcinoma in Italy: A national survey on clinical characteristics, diagnostic modalities and treatment. Results from the 'Cholangiocarcinoma' committee of the Italian Association for the Study of Liver disease. Digestive and Liver Disease. 2011;**43**:60-65. DOI: 10.1016/j.dld.2010.05.002

[9] Taylor-Robinson SD, Toledano MB, Arora S, Keegan TJ, Hargreaves S, et al. Increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales 1968-1998. Gut. 2001;**48**:816-820. DOI: 10.1136/gut.48.6.816

[10] Sempoux C, Jibara G, Ward SC, Fan C, Qin L, et al. Intrahepatic cholangiocarcinoma: New insights in pathology. Seminars in Liver Disease. 2011;**31**:49-60. DOI: 10.1055/s-0031-1272839

[11] Mosconi S, Beretta GD, Labianca R, Zampino MG, Gatta G, et al. Cholangiocarcinoma. Critical Reviews in Oncology/Hematology. 2009;**69**:259-270. DOI: 10.1016/j.critrevonc.2008.09.008

[12] Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, et al. AJCC Cancer Staging Manual. 8th ed. Switzerland: Springer Nature US; 2017

[13] Brierley J, Gospodarowicz MD, Wittekind CT. TNM Classification of Malignant Tumours, 8th Edition. Wiley-Blackwell; Dec 2016. ISBN: 978-1-119-26357-9

[14] DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, et al. Cholangiocarcinoma: Thirty-one-year experience with 564 patients at a single institution. Annals of Surgery. 2007;**245**:755-762. DOI: 10.1097/01.sla.0000251366.62632.d3

[15] Nakanuma Y, Sato Y, Harada K, Sasaki M, Xu J, et al. Pathological classification of intrahepatic cholangiocarcinoma based on a new concept. World Journal of Hepatology. 2010;**2**:419-427. DOI: 10.4254/wjh.v2.i12.419

[16] Aishima S, Oda Y. Pathogenesis and classification of intrahepatic cholangiocarcinoma: Different characters of perihilar large duct type versus peripheral small duct type. Journal of Hepato-Biliary-Pancreatic Sciences. 2015;**22**:94-100. DOI: 10.1002/jhbp.154

[17] Komuta M, Govaere O, Vandecaveye V, Akiba J, Van Steenbergen W, et al. Histological diversity in cholangiocellular carcinoma reflects the different cholangiocyte phenotypes. Hepatology. 2012;**55**:1876-1888. DOI: 10.1002/hep.25595

[18] Liau JY, Tsai JH, Yuan RH, Chang CN, Lee HJ, et al. Morphological subclassification of intrahepatic cholangiocarcinoma: Etiological, clinicopathological, and molecular features. Modern Pathology. 2014;**27**:1163-1173. DOI: 10.1038/modpathol.2013.241

[19] Carpino G, Cardinale V, Onori P, Franchitto A, Berloco PB, et al. Biliary tree stem/progenitor cells in glands of extrahepatic and intraheptic bile ducts: An anatomical in situ study yielding evidence of maturational lineages. Journal of Anatomy. 2012;**220**:186-199. DOI: 10.1111/j.1469-7580.2011.01462.x

[20] Turner R, Lozoya O, Wang Y, Cardinale V, Gaudio E, et al. Human hepatic stem cell and maturational liver lineage biology. Hepatology. 2011;**53**:1035-1045. DOI: 10.1002/hep.24157

[21] Blechacz B, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. Nature Reviews. Gastroenterology & Hepatology. 2011;**8**:512-522. DOI: 10.1038/nrgastro.2011.131

[22] Komuta M, Spee B, Vander Borght S, De Vos R, Verslype C, et al. Clinicopathological study on cholangiolocellular carcinoma suggesting hepatic progenitor cell origin. Hepatology. 2008;**47**:1544-1556. DOI: 10.1002/hep.22238

[23] Nakanuma Y, Xu J, Harada K, Sato Y, Sasaki M, et al. Pathological spectrum of intrahepatic cholangiocarcinoma arising in non-biliary chronic advanced liver diseases. Pathology International. 2011;**61**:298-305. DOI: 10.1111/j.1440-1827.2011.02665.x

[24] Claessen MMH, Vleggaar FP, Tytgat KMAJ, Siersema PD, van Buuren HR. High lifetime risk of cancer in primary sclerosing cholangitis. Journal of Hepatology. 2009;**50**:158-164. DOI: 10.1016/j.jhep.2008.08.013

[25] Chapman RW. Risk factors for biliary tract carcinogenesis. Annals of Oncology. 1999; **10**(Suppl 4):308-311. DOI: 10.1093/annonc/10.suppl_4.S308

[26] Shaib YH, Davila JA, McGlynn K, El-Serag HB. Rising incidence of intrahepatic cholangiocarcinoma in the United States: A true increase? Journal of Hepatology. 2004;**40**:472-477. DOI: 10.1016/j.jhep.2003.11.030

[27] Sahani D, Prasad SR, Tannabe KK, Hahn PF, Mueller PR, et al. Thorotrast-induced cholangiocarcinoma: Case report. Abdominal Imaging. 2003;**28**:72-74. DOI: 10.1007/s00261-001-0148-y

[28] Lipshutz GS, Brennan TV, Warren RS. Thorotrast-induced liver neoplasia: A collective review. Journal of the American College of Surgeons. 2002;**195**:713-718. DOI: 10.1016/S1072-7515(02)01287-5

[29] Aljiffry M, Abdulelah A, Walsh M, Peltekian K, Alwayn I, et al. Evidence-based approach to cholangiocarcinoma: A systematic review of the current literature. Journal of the American College of Surgeons. 2009;**208**:134-147. DOI: 10.1016/j.jamcollsurg.2008.09.007

[30] Sorensen HT, Friis S, Olsen JH, Thulstrup AM, Mellemkjaer L, et al. Risk of liver and other types of cancer in patients with cirrhosis: A nationwide cohort study in Denmark. Hepatology. 1998;**28**:921-925. DOI: 10.1002/hep.510280404

[31] Lee CH, Chang CJ, Lin YJ, Yeh CN, Chen MF, et al. Viral hepatitis-associated intrahepatic cholangiocarcinoma shares common disease processes with hepatocellular carcinoma. British Journal of Cancer. 2009;**100**:1765-1770. DOI: 10.1038/sj.bjc.6605063

[32] Kobayashi M, Ikeda K, Saitoh S, Suzuki F, Tsubota A, et al. Incidence of primary cholangiocellular carcinoma of the liver in japanese patients with Hepatitis C virus-related cirrhosis. Cancer. 2000;**88**:2471-2477. DOI: 10.1002/1097-0142(20000601)88:11<2471::AID-CNCR7>3.0.CO;2-T

[33] El-Serag HB, Engels EA, Landgren O, Chiao E, Henderson L, et al. Risk of hepatobiliary and pancreatic cancers after hepatitis C virus infection: A population-based study of U.S. veterans. Hepatology. 2009;**49**:116-123. DOI: 10.1002/hep.22606

[34] Shaib YH, El-Serag HB, Davila JA, Morgan R, Mcglynn KA. Risk factors of intrahepatic cholangiocarcinoma in the United States: A case-control study. Gastroenterology. 2005;**128**:620-626. DOI: 10.1053/j.gastro.2004.12.048

[35] Braconi C, Patel T. Cholangiocarcinoma: New insights into disease pathogenesis and biology. Infectious Disease Clinics of North America. 2010;**24**:871-884. DOI: 10.1016/j.idc.2010.07.006

[36] Fabris L, Cadamuro M, Moserle L, Dziura J, Cong X, et al. Nuclear expression of S100A4 calcium-binding protein increases cholangiocarcinoma invasiveness and metastasization. Hepatology. 2011;**54**:890-899. DOI: 10.1002/hep.24466

[37] Brivio S, Cadamuro M, Strazzabosco M, Fabris L. Tumor reactive stroma in cholangiocarcinoma: The fuel behind cancer aggressiveness. World Journal of Hepatology. 2017;**9**:455-468. DOI: 10.4254/wjh.v9.i9.455

[38] Dvorak HF, Senger DR, Dvorak AM. Fibrin as a component of the tumor stroma: Origins and biological significance. Cancer Metastasis Reviews. 1983;**2**:41-73. DOI: 10.1007/BF00046905

[39] Kalluri R, Zeisberg M. Fibroblasts in cancer. Nature Reviews. Cancer. 2006;**6**:392-401. DOI: 10.1038/nrc1877

[40] Albini A, Sporn MB. The tumour microenvironment as a target for chemoprevention. Nature Reviews Cancer. 2007;**7**:139-147. DOI: 10.1038/nrc2066

[41] Folkman J. Fundamental concepts of the angiogenic process. Current Molecular Medicine. 2003;**3**:643-651. DOI: 10.2174/1566524033479465

[42] Garin-Chesa P, Old LJ, Rettig WJ. Cell surface glycoprotein of reactive stromal fibroblasts as a potential antibody target in human epithelial cancers. Proceedings of the National Academy of Sciences. 1990;**87**:7235-7239. DOI: 10.1073/pnas.87.18.7235

[43] Xing F, Saidou J, Watabe K. Cancer associated fibroblasts (CAFs) in tumor microenvironment. Frontiers in Bioscience (Landmark edition). 2010;**15**:166-179. DOI: 10.2741/3613

[44] Thiery JP. Epithelial–mesenchymal transitions in tumour progression. Nature Reviews. Cancer. 2002;**2**:442-454. DOI: 10.1038/nrc822

[45] Bremnes RM, Dønnem T, Al-Saad S, Al-Shibli K, Andersen S, et al. The role of tumor stroma in cancer progression and prognosis: Emphasis on carcinoma-associated fibroblasts and non-small cell lung cancer. Journal of Thoracic Oncology. 2011;**6**:209-217. DOI: 10.1097/JTO.0b013e3181f8a1bd

[46] Kuperwasser C, Chavarria T, Wu M, Magrane G, Gray JW, et al. Reconstruction of functionally normal and malignant human breast tissues in mice. Proceedings of the National Academy of Sciences of the United States of America. 2004;**101**:4966-4971. DOI: 10.1073/pnas.0401064101

[47] Grum-Schwensen B, Klingelhofer J, Berg CH, El-Naaman C, Grigorian M, et al. Suppression of tumor development and metastasis formation in mice lacking the S100A4(mts1) gene. Cancer Research. 2005;**65**:3772-3780. DOI: 10.1158/0008-5472.CAN-04-4510

[48] Orimo A, Gupta PB, Sgroi DC, Arenzana-Seisdedos F, Delaunay T, et al. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. Cell. 2005;**121**:335-348. DOI: 10.1016/j.cell.2005.02.034

[49] Li G, Satyamoorthy K, Meier F, Berking C, Bogenrieder T, et al. Function and regulation of melanoma-stromal fibroblast interactions: When seeds meet soil. Oncogene. 2003; **22**:3162-3171. DOI: 10.1038/sj.onc.1206455

[50] Sulpice L, Rayar M, Desille M, Turlin B, Fautrel A, et al. Molecular profiling of stroma identifies osteopontin as an independent predictor of poor prognosis in intrahepatic cholangiocarcinoma. Hepatology. 2013;**58**:1992-2000. DOI: 10.1002/hep.26577

[51] Andersen JB, Spee B, Blechacz BR, Avital I, Komuta M, et al. Genomic and genetic characterization of cholangiocarcinoma identifies therapeutic targets for tyrosine kinase inhibitors. Gastroenterology. 2012;**142**(4):1021-1031.e15. DOI: 10.1053/j.gastro.2011.12.005

[52] Nishihara Y, Aishima S, Hayashi A, Iguchi T, Fujita N, et al. CD10+ fibroblasts are more involved in the progression of hilar/extrahepatic cholangiocarcinoma than of peripheral intrahepatic cholangiocarcinoma. Histopathology. 2009;**55**:423-431. DOI: 10.1111/j.1365-2559.2009.03398.x

[53] Chuaysri C, Thuwajit P, Paupairoj A, Chau-In S, Suthiphongchai T, et al. Alpha-smooth muscle actin-positive fibroblasts promote biliary cell proliferation and correlate with poor survival in cholangiocarcinoma. Oncology Reports. 2009;**21**:957-969. DOI: 10.3892/or_ 00000309

[54] Sirica AE. The role of cancer-associated myofibroblasts in intrahepatic cholangiocarcinoma. Nature Reviews Gastroenterology and Hepatology. 2012;**9**:44-54. DOI: 10.1038/ nrgastro.2011.222

[55] Dhanasekaran R, Hemming AW, Zendejas I, George T, Nelson DR, et al. Treatment outcomes and prognostic factors of intrahepatic cholangiocarcinoma. Oncology Reports. 2013;**29**:1259-1267. DOI: 10.3892/or.2013.2290

[56] Shen WF, Zhong W, Xu F, Kan T, Geng L, et al. Clinicopathological and prognostic analysis of 429 patients with intrahepatic cholangiocarcinoma. World Journal of Gastroenterology. 2009;**15**:5976-5982. DOI: 10.3748/wjg.15.5976

[57] Endo I, Gonen M, Yopp AC, Dalal KM, Zhou Q, et al. Intrahepatic cholangiocarcinoma: Rising frequency, improved survival, and determinants of outcome after resection. Annals of Surgery. 2008;**248**:84-96. DOI: 10.1097/SLA.0b013e318176c4d3

[58] Patel T. Cholangiocarcinoma-controversies and challenges. Nature Reviews. Gastroenterology & Hepatology. 2011;**8**:189-200. DOI: 10.1038/nrgastro.2011.20

[59] Lamerz R. Role of tumour markers, cytogenetics. Annals of Oncology. 1999;**10**(Suppl 4): 145-149

[60] Chung YE, Kim M-J, Park YN, Choi J-Y, Pyo JY, et al. Varying appearances of cholangiocarcinoma: Radiologic-pathologic correlation. Radiographics. 2009;**29**:683-700. DOI: 10.1148/rg.293085729

[61] Sainani NI, Catalano OA, Holalkere N-S, Zhu AX, Hahn PF, et al. Cholangiocarcinoma: Current and novel imaging techniques. Radiographics. 2008;**28**:1263-1287. DOI: 10.1148/rg.285075183

[62] Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, et al. Intrahepatic Cholangiocarcinoma: Expert consensus statement. HPB. 2015;**17**:669-680. DOI: 10.1111/hpb.12441

[63] Burkhart RA, Pawlik TM. Staging and prognostic models for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Cancer Control. 2017;**24**:107327481772923. DOI: 10.1177/1073274817729235

[64] Okabayashi T, Yamamoto J, Kosuge T, Shimada K, Yamasaki S, et al. A new staging system for mass-forming intrahepatic cholangiocarcinoma: Analysis of preoperative and postoperative variables. Cancer. 2001;**92**:2374-2383. DOI: 10.1002/1097-0142(20011101)92:9<2374::AID-CNCR1585>3.0.CO;2-L

[65] Yamasaki S. Intrahepatic cholangiocarcinoma: Macroscopic type and stage classification. Journal of Hepato-Biliary-Pancreatic Surgery. 2003;**10**:288-291. DOI: 10.1007/s00534-002-0732-8

[66] Nathan H, T a A, Vauthey J-N, Abdalla EK, Zhu AX, et al. A proposed staging system for intrahepatic cholangiocarcinoma. Annals of Surgical Oncology. 2009;**16**:14-22. DOI: 10.1245/s10434-008-0180-z

[67] Spolverato G, Bagante F, Weiss M, Alexandrescu S, Marques HP, et al. Comparative performances of the 7th and the 8th editions of the American Joint Committee on Cancer staging systems for intrahepatic cholangiocarcinoma. Journal of Surgical Oncology. May 2017;**115**(6):696-703. DOI: 10.1002/jso.24569

[68] Schreckenbach T, Liese J, Bechstein WO, Moench C. Posthepatectomy liver failure. Digestive Surgery. 2012;**29**:79-85. DOI: 10.1159/000335741

[69] Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, et al. Surgical resection of hepatic metastases from colorectal cancer: A systematic review of published studies. British Journal of Cancer. 2006;**94**:982-999. DOI: 10.1038/sj.bjc.6603033

[70] Van Den Broek MAJ, Olde Damink SWM, Dejong CHC, Lang H, Malagó M, et al. Liver failure after partial hepatic resection: Definition, pathophysiology, risk factors and treatment. Liver International. 2008;**28**:767-780. DOI: 10.1111/j.1478-3231.2008.01777.x

[71] Van Der Vorst JR, Van Dam RM, Van Stiphout RSA, Van Den Broek MA, Hollander IH, et al. Virtual liver resection and volumetric analysis of the future liver remnant using open source image processing software. World Journal of Surgery. 2010;**34**:2426-2433. DOI: 10.1007/s00268-010-0663-5

[72] Dello SAWG, Van Dam RM, Slangen JJG, Van De Poll MCG, Bemelmans MHA, et al. Liver volumetry plug and play: Do it yourself with ImageJ. World Journal of Surgery. 2007;**31**:2215-2221. DOI: 10.1007/s00268-007-9197-x

[73] Dello SAWG, Stoot JHMB, Van Stiphout RSA, Bloemen JG, Wigmore SJ, et al. Prospective volumetric assessment of the liver on a personal computer by nonradiologists prior to partial hepatectomy. World Journal of Surgery. 2011;**35**:386-392. DOI: 10.1007/s00268-010-0877-6

[74] Schindl MJ, Redhead DN, Fearon KCH, Garden OJ, Wigmore SJ. The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. Gut. 2005;**54**:289-296. DOI: 10.1136/gut.2004.046524

[75] Haimerl M, Verloh N, Fellner C, Zeman F, Teufel A, et al. MRI-based estimation of liver function: Gd-EOB-DTPA-enhanced T1 relaxometry of 3T vs. The MELD score. Scientific Reports. 2014;**4**:5621. DOI: 10.1038/srep05621

[76] Watanabe Y, Kurmon K. Assessment by pulse dye-densitometry indocyanine green (ICG) clearance test of hepatic function of patients before cardiac surgery: Its value as a predictor of serious postoperative liver dysfunction. Journal of Cardiothoracic and Vascular Anesthesia. 1999;**13**:299-303. DOI: 10.1016/S1053-0770(99)90267-7

[77] Kagawa T, Adachi Y, Hashimoto N, Mitsui H, Ohashi T, et al. Loss of organic anion transporting polypeptide 1B3 function causes marked delay in indocyanine green clearance without any clinical symptoms. Hepatology. 2017;**65**:1065-1068. DOI: 10.1002/hep.28950

[78] Su CH, Tsay SH, Wu CC, Shyr YM, King KL, et al. Factors influencing postoperative morbidity, mortality, and survival after resection for hilar cholangiocarcinoma. Annals of Surgery. 1996;**223**:384-394. DOI: 10.1097/00000658-199604000-00007

[79] Wang K, Zhang H, Xia Y, Liu J, Shen F. Surgical options for intrahepatic cholangiocarcinoma. Hepatobiliary Surgery and Nutrition. 2017;**6**:79-90. DOI: 10.21037/hbsn.2017.01.06

[80] yong LY, Li H, Lv P, Liu G, rong LX, et al. Prognostic value of cirrhosis for intrahepatic cholangiocarcinoma after surgical treatment. Journal of Gastrointestinal Surgery. 2011;**15**:608-613. DOI: 10.1007/s11605-011-1419-8

[81] Sapisochin G, Fidelman N, Roberts JP, Yao FY. Mixed hepatocellular cholangiocarcinoma and intrahepatic cholangiocarcinoma in patients undergoing transplantation for hepatocellular carcinoma. Liver Transplant. 2011;**17**:934-942. DOI: 10.1002/lt.22307

[82] Ali SM, Clark CJ, Zaydfudim VM, Que FG, Nagorney DM. Role of major vascular resection in patients with intrahepatic cholangiocarcinoma. Annals of Surgical Oncology. 2013;**20**:2023-2028. DOI: 10.1245/s10434-012-2808-2

[83] Lang H, Sotiropoulos GC, Sgourakis G, Schmitz KJ, Paul A, et al. Operations for intrahepatic cholangiocarcinoma: Single-institution experience of 158 patients. Journal of the American College of Surgeons. 2009;**208**:218-228. DOI: 10.1016/j.jamcollsurg.2008.10.017

[84] Spolverato G, Kim Y, Alexandrescu S, Marques HP, Lamelas J, et al. Management and outcomes of patients with recurrent intrahepatic cholangiocarcinoma following previous curative-intent surgical resection. Annals of Surgical Oncology. 2016;**23**:235-243. DOI: 10.1245/s10434-015-4642-9

[85] Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma. JAMA Surgery. 2014;**149**:565. DOI: 10.1001/jamasurg.2013.5137

[86] Koay EJ, Odisio BC, Javle M, Vauthey J-N, Crane CH. Management of unresectable intrahepatic cholangiocarcinoma: How do we decide among the various liver-directed treatments? Hepatobiliary Surgery and Nutrition. 2017;**6**:105-116. DOI: 10.21037/hbsn.2017.01.16

[87] Kim JH, Yoon H-K, Ko G-Y, Gwon DI, Jang CS, et al. Nonresectable combined hepatocellular carcinoma and cholangiocarcinoma: Analysis of the response and prognostic factors after transcatheter arterial chemoembolization. Radiology. 2010;**255**:270-277. DOI: 10.1148/radiol.09091076

[88] Aliberti C, Benea G, Tilli M, Fiorentini G. Chemoembolization (TACE) of unresectable intrahepatic cholangiocarcinoma with slow-release doxorubicin-eluting beads: Preliminary results. Cardiovascular and Interventional Radiology. 2008;**31**:883-888. DOI: 10.1007/s00270-008-9336-2

[89] Herber S, Otto G, Schneider J, Manzl N, Kummer I, et al. Transarterial chemoembolization (TACE) for inoperable intrahepatic cholangiocarcinoma. Cardiovascular and Interventional Radiology. 2007;**30**:1156-1165. DOI: 10.1007/s00270-007-9032-7

[90] Burger I, Hong K, Schulick R, Georgiades C, Thuluvath P, et al. Transcatheter arterial chemoembolization in unresectable cholangiocarcinoma: Initial experience in a single institution. Journal of Vascular and Interventional Radiology. 2005;**16**:353-361. DOI: 10.1097/01.RVI.0000143768.60751.78

[91] Poggi G, Amatu A, Montagna B, Quaretti P, Minoia C, et al. OEM-TACE: A new therapeutic approach in unresectable intrahepatic cholangiocarcinoma. Cardiovascular and Interventional Radiology. 2009;**32**:1187-1192. DOI: 10.1007/s00270-009-9694-4

[92] Kiefer MV, Albert M, McNally M, Robertson M, Sun W, et al. Chemoembolization of intrahepatic cholangiocarcinoma with cisplatinum, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol. Cancer. 2011;**117**:1498-1505. DOI: 10.1002/cncr.25625

[93] Al-Adra DP, Gill RS, Axford SJ, Shi X, Kneteman N, et al. Treatment of unresectable intrahepatic cholangiocarcinoma with yttrium-90 radioembolization: A systematic review and pooled analysis. European Journal of Surgical Oncology. 2015;**41**:120-127. DOI: 10.1016/j.ejso.2014.07.007

[94] Han K, Ko HK, Kim KW, Won HJ, Shin YM, et al. Radiofrequency ablation in the treatment of unresectable intrahepatic cholangiocarcinoma: Systematic review and meta-analysis. Journal of Vascular and Interventional Radiology. 2015;**26**:943-948. DOI: 10.1016/j.jvir.2015.02.024

[95] Yu MA, Liang P, Yu XL, Cheng ZG, Han ZY, et al. Sonography-guided percutaneous microwave ablation of intrahepatic primary cholangiocarcinoma. European Journal of Radiology. 2011;**80**:548-552. DOI: 10.1016/j.ejrad.2011.01.014

[96] Rizvi S, Gores GJ. Emerging molecular therapeutic targets for cholangiocarcinoma. Journal of Hepatology. 2017;**67**:632-644. DOI: 10.1016/j.jhep.2017.03.026

[97] Tao R, Krishnan S, Bhosale PR, Javle MM, Aloia TA, et al. Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: A retrospective dose response analysis. Journal of Clinical Oncology. 2016;**34**:219-226. DOI: 10.1200/JCO.2015.61.3778

[98] Hong TS, Wo JY, Yeap BY, Ben-Josef E, McDonnell EI, et al. Multi-institutional phase II study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Journal of Clinical Oncology. 2016;**34**:460-468. DOI: 10.1200/JCO.2015.64.2710

[99] Jarnagin WR, Schwartz LH, Gultekin DH, Gönen M, Haviland D, et al. Regional chemotherapy for unresectable primary liver cancer: Results of a phase II clinical trial and assessment of DCE-MRI as a biomarker of survival. Annals of Oncology. 2009;**20**:1589-1595. DOI: 10.1093/annonc/mdp029

[100] Kemeny NE, Schwartz L, Gönen M, Yopp A, Gultekin D, et al. Treating primary liver cancer with hepatic arterial infusion of floxuridine and dexamethasone: Does the addition of systemic bevacizumab improve results? Oncology. 2011;**80**:153-159. DOI: 10.1159/000324704

[101] Massani M, Nistri C, Ruffolo C, Bonariol R, Pauletti B, et al. Intrahepatic chemotherapy for unresectable cholangiocarcinoma: Review of literature and personal experience. Updates in Surgery. 2015;**67**:389-400. DOI: 10.1007/s13304-015-0330-3

[102] Rahnemai-Azar AA, Weisbrod AB, Dillhoff M, Schmidt C, Pawlik TM. Intrahepatic cholangiocarcinoma: Current management and emerging therapies. Expert Review of Gastroenterology & Hepatology. 2017;**11**:439-449. DOI: 10.1080/17474124.2017.1309290

[103] Squadroni M, Tondulli L, Gatta G, Mosconi S, Beretta G, et al. Cholangiocarcinoma. Critical Reviews in Oncology/Hematology. 2017;**116**:11-31. DOI: 10.1016/j.critrevonc.2016.11.012

[104] Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: A systematic review and meta-analysis. Journal of Clinical Oncology. 2012;**30**:1934-1940. DOI: 10.1200/JCO.2011.40.5381

[105] Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. The New England Journal of Medicine. 2010;**362**:1273-1281. DOI: 10.1056/NEJMoa0908721

[106] Novarino AMT, Satolli MA, Chiappino I, Giacobino A, Napoletano R, et al. FOLFOX-4 regimen or single-agent gemcitabine as first-line chemotherapy in advanced biliary tract cancer. American Journal of Clinical Oncology Cancer Clinical Trials. 2013;**36**:466-471. DOI: 10.1097/COC.0b013e31825691c3

[107] Lee J, Hong TH, Lee IS, You YK, Lee MA. Comparison of the efficacy between gemcitabine-cisplatin and capecitabine-cisplatin combination chemotherapy for advanced biliary tract cancer. Cancer Research and Treatment. 2014;**47**:259-265. DOI: 10.4143/crt.2013.230

[108] Croitoru A, Gramaticu I, Dinu I, Gheorghe L, Alexandrescu S, et al. Fluoropyrimidines plus cisplatin versus gemcitabine/gemcitabine plus cisplatin in locally advanced and metastatic biliary tract carcinoma—A retrospective study. Journal of Gastrointestinal and Liver Diseases. 2012;**21**:277-284

[109] Iyer RV, Gibbs J, Kuvshinoff B, Fakih M, Kepner J, et al. A phase II study of gemcitabine and capecitabine in advanced cholangiocarcinoma and carcinoma of the gallbladder: A single-institution prospective study. Annals of Surgical Oncology. 2007;**14**:3202-3209. DOI: 10.1245/s10434-007-9539-9

[110] Yamashita Y, Taketomi A, Itoh S, Harimoto N, Tsujita E, et al. Phase II trial of gemcitabine combined with 5-fluorouracil and cisplatin (GFP) chemotherapy in patients with advanced biliary tree cancers. Japanese Journal of Clinical Oncology. 2009;**40**:24-28. DOI: 10.1093/jjco/hyp119

[111] Cereda S, Passoni P, Reni M, Viganò MG, Aldrighetti L, et al. The cisplatin, epirubicin, 5-fluorouracil, gemcitabine (PEFG) regimen in advanced biliary tract adenocarcinoma. Cancer. 2010;**116**:2208-2214. DOI: 10.1002/cncr.24970

[112] Borbath I, Ceratti A, Verslype C, Demols A, Delaunoit T, et al. Combination of gemcitabine and cetuximab in patients with advanced cholangiocarcinoma: A phase II study of the belgian group of digestive oncology. Annals of Oncology. 2013;**24**:2824-2829. DOI: 10.1093/annonc/mdt337

[113] Rubovszky G, Láng I, Ganofszky E, Horváth Z, Juhos E, et al. Cetuximab, gemcitabine and capecitabine in patients with inoperable biliary tract cancer: A phase 2 study. European Journal of Cancer. 2013;**49**:3806-3812. DOI: 10.1016/j.ejca.2013.07.143

[114] Gruenberger B, Schueller J, Heubrandtner U, Wrba F, Tamandl D, et al. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: A phase 2 study. The Lancet Oncology. 2010;**11**:1142-1148. DOI: 10.1016/S1470-2045(10)70247-3

IntechOpen

IntechOpen