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Chapter

Bile Duct Cancer: Preoperative Evaluation and Management

Tommaso Stecca, Bruno Pauletti, Luca Bonariol, Ezio Caratozzolo and Marco Massani

Abstract

Cholangiocarcinomas (CCAs) are malignant tumors that can develop anywhere along the biliary tree. Almost 10% of cholangiocarcinomas arise from the intrahepatic bile ducts (iCCA); 50–60% from the bifurcation of the hepatic duct (perhilar cholangiocarcinoma, pCCA); and 20–30% from the distal bile duct (dCCA). The 7th edition of the AJCC staging system, released in 2010, divides the tumors into two major categories: perihilar (pCCA) and distal (dCCA) cholangiocarcinoma, given the differences in anatomy of the bile duct and consideration of local factors related to resectability. There are separate histological classifications for intrahepatic and extrahepatic cholangiocarcinoma. The majority of CCAs (90%) are well or moderately differentiated adenocarcinomas. Other features include invasiveness with early neural, perineural, periductal and lymphatic infiltration (more than 50% of cases at diagnosis) and longitudinal subepithelial infiltration along the wall of the bile duct up to 2 cm proximally and 1 cm distally. In this chapter the extrhepatic bile duct cancers are analyzed.

Keywords: bile duct, cancer, embolization, drainage

1. Introduction

Cholangiocarcinomas (CCAs) are malignant tumors that can develop anywhere along the biliary tree [1]. Almost 10% of cholangiocarcinomas arise from the intrahepatic bile ducts (iCCA); 50–60% from the bifurcation of the hepatic duct (perihilar cholangiocarcinoma, pCCA), previously called Klatskin from the name of the author who first described it in 1965; and 20–30% from the distal bile duct (dCCA) [2]. In the previous editions of the American Joint Committee on Cancer (AJCC), staging system of extrahepatic bile duct tumors has been considered as a single entity [3]. The seventh edition of the AJCC staging system, released in 2010, divides the tumors into two major categories: perihilar cholangiocarcinoma (pCCA) and distal cholangiocarcinoma (dCCA) [4], given the differences in anatomy of the bile duct and consideration of local factors related to resectability [5]. For epidemiological findings it is advisable to avoid misclassification and to define subtypes according to the WHO classification as iCCA, pCCA, and dCCA [6–8].

There are separate histological classifications for intrahepatic and extrahepatic cholangiocarcinoma. The majority of CCAs (90%) are well- or moderately differentiated adenocarcinomas with a tendency to develop intense desmoplastic reactions due to the rapid proliferation of the tumor-associated stromal cells and

cancer-associated fibroblasts. Other features include invasiveness with early neural, perineural, periductal, and lymphatic infiltration (more than 50% of cases at diagnosis) and longitudinal subepithelial infiltration along the wall of the bile duct up to 2 cm proximally and 1 cm distally [9].

Although there is little data on this neoplasm, incidence rates and mortality seem to be declining in many countries. Through analysis of the SEER database, the mortality rate in the United States fell from 0.6 to 0.3 per 100,000 and incidence rates from 1.08 to 0.82 per 100,000. These data are probably more difficult to obtain because of the common ICD classification for both gallbladder and extrahepatic CCA tumors [10].

pCCA is the most common form with variable prevalence according to geographic areas, between 46 and 97% [4, 11, 12]. pCCA is diagnosed earlier and smaller than the intrahepatic variant because of its early presentation with indolent jaundice in 90% of cases or with cholangitis in about 10%. The infiltrative periductal histotype is the most common form; the exophytic mass-forming or intraductal papillary is less frequent [13]. Distal cholangiocarcinoma (dCCA) may derive from two precursors, recognized in the last WHO classification: intraductal papillary neoplasia and biliary intraepithelial neoplasia [14]. Similar to the pCCA, patients present at the onset of cholestatic jaundice and cholangitis secondary to biliary obstruction.

The prognosis is generally poor with a 5-year survival that is less than 5%. The median survival rate for patients with the intrahepatic variant is between 18 and 30 months; however, the perihilar variant has a median between 14 and 24 months. The only curative therapeutic option can be expected from liver surgery for early-stage tumors. After surgery, the recurrence rate is between 60 and 90%. However, given that most patients come to the attention of the surgeon with an advanced stage of disease, thus precluding the surgical option, 75% of patients die 1 year after diagnosis. The main causes of death among patients are cachexia, liver failure, and sepsis due to biliary tract obstruction. Although 1-year survival increased from 16% (1975–1979) to 28% (1995–1999), the 5-year survival showed no significant change [2].

2. Preoperative biliary drainage

2.1 Obstructive jaundice

Biliary obstruction leads to numerous pathophysiological consequences both at a local level, in the biliary tree, and at a systemic one. Affected patients are at high risk of liver insufficiency, renal failure, heart failure, coagulopathy, immunodeficiency, infectious complications, and, therefore, increased morbidity and mortality [15].

2.1.1 Local effects

Pressure inside the biliary tree is normally between 5 and 10 cmH_2O, but in case of complete obstruction, it can reach 30 cmH_2O. The biliary secretion is prevented when it exceeds the value of 10 cmH_2O [16]. Cholestasis favors bacterial overgrowth of the bile which, under normal conditions, is sterile. Furthermore, biliary hypertension causes a "cholangio-venous" reflux sustained by the increased permeability of bile ductules, thus favoring bacterial translocation and finally severe infections and sepsis [17, 18], as well as periportal neutrophilic infiltrate [19].

Increased pressure in the biliary system can gradually reduce the production of bile. However, the risk of lithogenesis is low due to the greater reduction in the secretion of cholesterol and phospholipids than bile salts (which guarantee the

solubility of cholesterol in the bile). When the obstruction is resolved, the restoration of cholesterol and phospholipid secretion is inversely faster than the bile salt ones, thus favoring the lithogenesis responsible for the early obstruction of biliary stents [19, 20].

2.1.2 Systemic effects

Jaundice influences liver metabolic and synthetic function. The inhibition of cytochrome P450 and the reduction of aerobic and oxidative metabolism lead to an increase in oxidative stress, cell apoptosis, and alteration of drug metabolism. The reduced liver synthetic capacity leads to a reduction in the levels of albumin, coagulation factors, and immunoglobulins [20].

The proliferation of the intestinal microbial flora is favored by the interruption of the recirculation of the bile salts and is associated with the dysfunction of the intestinal mucosal barrier and the bacterial translocation with consequent increase in the absorption of endotoxins hereby produced [19]. Increased intestinal permeability also plays a key role in the development of a potential septic state and renal complications [21].

Endotoxin (lipopolysaccharide) is usually inactivated by the hepatic reticuloendothelial system, but organ dysfunction—associated with increased endogenous production—leads to a systemic inflammatory response syndrome (SIRS) that may result in the multi-organ dysfunction syndrome (hemodynamic instability and renal failure) [22–25].

Acute renal failure occurs in 10% of jaundiced patients. This complication is associated with high mortality (70–80%). In addition, endotoxinemia stimulates the secretion of vasoactive prostaglandins and cytokines that are responsible for tubular necrosis and fibrin deposition with further reduction of glomerular filtration [26–28].

The alteration of the immune system and the septic manifestations are mainly due to the insufficiency of the cellular immunity (T lymphocytes) induced by the release of cytokines (TNFα, IL-1, IL-6, IFNɣ), prostaglandins, and other mediators of inflammation [29–31].

The hemorrhagic diathesis is due to coagulation disorders induced by both complement activation and reduced hepatic prothrombin and other vitamin K-dependent factors (VII, IX, X, C-S-Z protein synthesis). The absence of bile salts in the intestine prevents the absorption of vitamin K [32].

2.2 Guidelines

2.2.1 Perihilar cholangiocarcinoma

In patients with perihilar cholangiocarcinoma and jaundice, the National Comprehensive Cancer Network (NCCN) guidelines recommend to consider preoperative biliary drainage. The decision should be always made by a multidisciplinary team at an HPB center. The different expertise of the different centers significantly affects the choice between the endoscopic and the percutaneous approach. Bile drainage can be performed either endoscopically or percutaneously. There are currently no randomized clinical trials comparing these two types of drainage. Most retrospective studies have not shown any significant differences, both in terms of bilirubinemia reduction and complications [33]. The effectiveness of preoperative biliary drainage was analyzed by Farges et al. [34] in a multicenter retrospective study performed on 366 patients who underwent pCCA resection between 1997 and 2008 with right or left hepatectomy without resection of the

pancreatic head. One hundred and eighty patients (180/366; 49.1%) received biliary drain placement. Although drainage did not result in a significant change in postoperative mortality, a subanalysis showed a decrease in normalized postoperative mortality for preoperative bilirubin in patients undergoing right hepatectomy (adjusted OR = 0.29; CI 0.11–0.77; p = 0.013) and an increase in postoperative mortality in patients undergoing left hepatectomy (OR = 4.06 CI 1.01–16.3; p = 0.035). In particular, the cause of major postoperative mortality in the right hepatectomy group was liver failure and sepsis in the left hepatectomy group. Endoscopic nasobiliary drainage seems to be the most appropriate method of PBD in terms of minimizing the risks of tract seeding and inflammatory reactions [33].

2.2.2 Distal cholangiocarcinoma

The latest guidelines issued by the NCCN for the endoscopic treatment of biliary obstruction in dCCA recommend different treatments based on clinical status (**Table 1**) [35].

One of the reasons for greater debate concerns the balance between risks and benefits in the preoperative stenting of neoplastic biliary obstruction in resectable patients. The meta-analyses that investigated this topic concluded that preoperative biliary drainage should not be performed routinely, given the absence of difference in mortality but, above all, the increased associated morbidity [36–39]. However, stenting is recommended in patients with cholangitis, pruritus, coagulopathy, and renal failure or for whom surgical treatment is delayed for at least 1 week [35]. The scientific debate is also open regarding the type of stent, plastic or metal (partially or completely coated). It has been shown that coated metal stents have a lower dislocation rate and a longer patency time [40]. On the other hand, plastic stents are easier to position or replace and have an advantageous cost-benefit profile. However, a recent meta-analysis has shown that in patients with an overall survival of more than 6 months, the placement of the metal stent is associated with a better cost-benefit and quality of life [41]. Patency duration, morbidity, mortality, and repositioning rates were investigated in other studies [42–45] that demonstrated the superiority of the metal stent (short intrapancreatic or coated) due to increased patency resulting in a reduced need for additional endoscopy. The guidelines compiled by the NCCN and the European Society of Gastrointestinal Endoscopy (ESGE) indicate as a first choice the plastic stent in patients diagnosed with uncertain malignancy and those with an unfavorable prognosis (≤3 months according to NCCN; ≤4 months according to ESGE) [35, 46].

Status	Recommendation
Resectable tumor, jaundice	Preoperative biliary drainage only in symptomatic patients (cholangitis, fever, pruritus, sepsis, coagulopathy, renal failure) or in which the surgical program is delayed by at least 1 week Plastic or metal stent (if diagnosis histologically confirmed)
"Borderline resectable" tumor, candidate for neoadjuvant therapy, jaundice	Self-expanding metal stent
Unresectable tumor, intraoperative finding, jaundice	Self-expanding metal stent if no surgical bypass is performed during surgery
Metastatic tumor, jaundice	Self-expanding metal stent*

**Many members of the NCCN panel point to the plastic stent in patients with a life expectancy of less than 3 months.*

Table 1.
Neoplastic biliary obstruction. NCCN endoscopic treatment guidelines.

3. Liver function tests

pCCA surgical approach may also require extended liver resection. The hepatic parenchyma must be removed, but also the residual volume and its ability to guarantee acceptable residual liver function must be carefully assessed [47]. In 2011 the International Study Group of Liver Surgery published and updated the posthepatectomy liver failure definition and grading [48]. Posthepatectomy liver failure (PHLF) has been defined as an "acquired deterioration in the ability of the liver to maintain its synthetic, excretory and detoxifying functions, characterized by an increased INR, and hyperbilirubinemia on or after postoperative day 5." PHLF is then differentiated into three grades (A, B, and C) based on clinical and invasive management [48]. The presence of liver disease and liver function correlates with the critical residual liver volume able to predict PHLF. The limit for a safe resection ranges from 20 to 30% future remnant liver among patients with normal liver function. However, this limit must be raised to over 40% in case of risk factors related to patient, liver, or surgery [47].

3.1 Volumetry

Computed tomography and magnetic resonance imaging are used increasingly to measure liver volume in patients evaluated for resection. Numerous factors can influence the accuracy of preoperative liver volumetry: the phase of contrast administration, slice thickness, use of CT versus MRI, varying image processing software, and inter-user variability, as well as the degree to which non-parenchymal structures are erroneously included within the functional liver volume [49].

In 2002 Vauthey published the formula to estimate total liver volume (TLV) based on body surface area (BSA). The formula obtained was TLV = 794.41 + 1267.28 × BSA (m^2), and a formula based on patient weight also was derived: TLV = 191.80 + 18.51 × weight (kg) [50].

In 2015 Martel compared the two techniques, the measured and the estimated liver volume, to determine the accuracy and variability of each volumetric method [49]. The conclusion of his study is that TLV is best evaluated by direct radiologic measurement rather than by indirect estimation. Indeed, estimated volumetry leads to a clinically significant over- or underestimation of the future liver remnant (≥5% in 31.9% of patients) and is more frequently associated with an underestimation of the estimated TLV and an overestimation of the estimated remnant future liver ratio [49].

3.2 Indocyanine green clearance test

Many quantitative liver function tests have been proposed, but they are impractical in a clinical setting because of excessive cost, need for multiple samples and prolonged catheterization, and risk of allergic reaction. Indocyanine green (ICG) clearance test is considered the most predictive test of operative mortality after hepatectomy if compared to other tests such as the amino acid clearance test or aminopyrine breath test [51]. The indocyanine green dye is absorbed by the hepatocytes and excreted via the biliary tract without enterohepatic recirculation. The percentage of retention can be measured by pulsed spectrophotometry using an optical sensor [52]. The $ICGR_{15}$ describes the percentage of circulatory retention of indocyanine green during the first 15 min after bolus injection. The cutoff value of ICG retention normal value in healthy patients is between 8 and 15%, and the cutoff value that allows a major hepatectomy is between 14 and 17% [53, 54]. Minor resections may be performed for values that reach 22% and limited hepatectomies

(bisegmentectomies) to values up to 40%. Some authors claim that laparoscopic limited wedge resections could be tolerated for values even greater [55]. Bilirubin and indocyanine green bind to the same carrier in the transport phase in hepatocytes, determining a competitive inhibition. For that reason, ICG retention is not valid in jaundiced patients.

4. Portal vein embolization

Portal vein embolization (PVE) is indicated in patients in whom a major resection or a parenchymal resection of more than 50–60% of the TLV is programmed, with the goal to prevent or reduce the risk of posthepatectomy liver failure [Benson 2014]. Although there are no randomized trials comparing the operative risk in patients subjected or not to PVE, a reduction in mortality is demonstrated from the retrospective series present in the literature in up to 0–2% of patients resected after PVE [Benson 2014]. In contrast, mortality rates vary between 10 and 21% in HPB centers where the indication to the PVE has been given with a residual liver volume less than 25–30%.

5. Preoperative staging systems

5.1 Perihilar cholangiocarcinoma

The Bismuth-Corlette classification is the most used to program the best derivative approach because it evaluates the longitudinal tumor extension. Four types of pCCA are distinguished based on their perihilar extension: type I, tumor confined to the common hepatic duct; type II, tumor limited to the confluence of the hepatic duct, without involvement of the second-order ducts; type III, tumor involving the confluence with extension to the right (IIIA) or left (IIIB) hepatic duct; and type IV, tumor affecting the biliary confluence with the involvement of secondary intrahepatic ducts on both sides. This system is used to plan the surgical treatment, from the resection (type I and II) to a major hepatectomy (type III). Type IV is traditionally considered nonsurgical, except for liver transplantation [56], but recently, curative surgery has also been attempted in type IV tumors that extend backward for less than 2 cm from the hilum. However, the Bismuth-Corlette classification system lacks important resectability information such as vascular infiltration, local or distant lymph node metastatic spread, and lobar hepatic atrophy, and therefore this system has no prognostic value and does not correlate with survival results [57, 58]. Moreover, in some cases, a precise Bismuth-Corlette classification can be difficult to define at the imaging due to the poor definition of the longitudinal extension in case of subepithelial infiltration (infiltrative forms) or of mucosal diffusion (papillary polypoid forms) [13].

The classification proposed by the Memorial Sloan-Kettering Cancer Center (MSKCC) details three factors related to tumor extension: the position and extent of biliary involvement (similar to the Bismuth-Corlette classification), portal vein invasion, and hepatic lobar atrophy, independently of lymph node or distant metastases. It is used for the selection of patients fit for surgery [59].

In the seventh edition of the AJCC/UICC staging system, the pCCA was staged as a separate entity based on anatomo-pathological staging (pathological TNM). The AJCC system also considers involvement of the portal vein and hepatic artery, lymph node status, and distant metastases. It is mainly used as a postoperative staging system and has a minimal utility to assess the resectability. An initial stage tumor (T1) is limited to the bile duct wall. T2 tumors extend beyond the bile duct wall, invading the periductal fat (T2a) or liver (T2b), and often present as

periductal infiltrative forms or as a nodular mass showing irregular duct wall thickening with contrast enhancement. The T3 stage includes locally invasive lesions involving the liver, gallbladder, pancreas, or ipsilateral portal vein or hepatic artery. The T4 stage includes widely invasive tumors, with bilateral extension to the portal vein or to the main portal trunk, the common hepatic artery, the contralateral vascular extension, and the involvement of the second-order bile ducts or to adjacent organs (colon, stomach, duodenum, or abdominal wall). The involvement of the hepatic parenchyma is classified as T2 instead of T3 since parenchymal involvement alone has a better prognosis than unilateral vascular involvement.

Numerous experiences have shown inaccuracies offered by the AJCC system, which may, in part, be due to not having taken into account the depth of the tumor invasion [60]. Given the limitations of the various staging systems and the difficulty in comparing the results in various centers, DeOliveira and an international panel of experts have introduced a new staging system for the pCCA, which also includes new factors to improve and standardize the determination of prognosis and tumor reporting [61]. This new system is derived from the Bismuth-Corlette classification for the evaluation of the involvement of the biliary tree but also considers (a) the size of the tumor (diameter >1 cm, 1–3 cm, or ≥3 cm); (b) tumor morphology, periductal or nodular-sclerosing or mass-forming, intraductal or polypoid, and mixed; (c) degree and position of the hepatic artery infiltration and of the portal vein encasement; (d) hepatic lobar atrophy and future liver remnant volume; (e) other liver diseases (fibrosis, nonalcoholic steatohepatitis, or PSC); (f) lymph nodes; and (g) distant metastases, including the liver and peritoneal ones. Therefore, this staging is applicable in the preoperative setting and includes well-established prognostic factors. The inclusion of the type of macroscopic tumor growth has never been included in other staging systems and has been shown to be a predictor of survival [62]. However, this staging system is rather complicated and also includes some prognostic factors not yet validated, such as tumor size, lobar atrophy, and the volumetric analysis [59]. The validity of this new system still needs verification in large prospective studies.

5.2 Distal cholangiocarcinoma

The first classification system that has assigned a definition for the dCCA separated from the pCCA is the seventh edition of the AJCC/UICC classification. This has been an important step because the differences between the two extrahepatic forms have been recognized. For example, the depth of ductal invasion and pancreatic invasion is significantly more common in dCCA [63]. Indeed, depth of invasion, lymph node metastasis, perineural and microscopic vascular invasion as well as the invasion of the pancreas, and the R0 resection are significant survival predictors [64, 65]. The pattern of lymph node metastasis differs between the three types of CCA and is most commonly observed in the dCCA [66]. Several studies have suggested that the number of pathological lymph nodes is an independent prognostic factor; more than two metastatic lymph nodes are predictive of a worse prognosis. In the AJCC classification, the T stage distinguishes T1 and T2 tumors based on the microscopic tumor growth pattern if confined to the bile duct or beyond it. The TNM staging system shares some of the features of the pCCA: T1 and T2 tumors are confined to the bile duct wall (T1) or invade the bile duct without invasion to adjacent organs (T2). Invasion of adjacent organs (pancreas, stomach, and duodenum) is considered T3. The invasion of the celiac tripod and superior mesenteric artery is considered T4. Moreover, the TNM classification presents similarities with that of pancreatic cancer. The lymph node staging has two stages (N0 and N1). Unlike proximal tumors, lymph node staging is performed at the time of surgery with the sampling of at least 12 lymph nodes.

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