BILE DUCTS

Treatment of Cholangiocarcinoma

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Problem: Cholangiocarcinoma is the second most common primary liver cancer, which may arise at any point in the biliary tree. It can be divided into three principal types: intrahepatic, hilar and distal, requiring different diagnostic and therapeutic approaches.

Methods: Review the clinico-morphological diagnostic and surgical aspects in the literature for each type of cholangiocarcinoma.

Results: Intrahepatic cholangiocarcinoma is discovered at an advanced stage. It is generally a large fibrous non-encapsulated heterogeneous tumors miming metastatic adenocarcinoma. One third of the patients are resectable. Curative treatment includes major hepatectomy with extensive hepatoduodenal lymphadenectomy. Hilar cholangiocarcinoma includes proximal bile duct tumors usually discovered in jaundiced patients. When the portal vein and the hepatic artery are involved the surgical resection require vascular reconstruction. Distal cholangiocarcinoma includes the tumors located in the common bile duct. The association with lymph node and perineural invasion requiring the resection of the extrahepatic bile duct with lymphadenectomy and in some cases pancreaticoduodenectomy.

Resolution and scientific novelty: The only curative treatment for all types of cholangiocarcinoma is surgical resection. Better preoperative imaging assessment, percutaneous transhepatic biliary drainage and preoperative portal vein embolization has led to increase the rate of resectability. In unresectable cases, percutaneous or endoscopic stenting is preferred to surgical palliative bypass procedure. Each type of cholangiocarcinoma requires a specialized diagnostic and therapeutic approaches. The extent of resection remains controversial: progress in survival was obtained by combining the hepatic resection including the removal of caudate lobe associated in some cases to portal vein reconstruction to the bile duct resection with large lymphadenectomy. In patients with distal cholangiocarcinoma, the progress may by obtained by combining the bile duct resection with pancreatoduodenectomy realizing a complete lymphadenectomy. Also the challenge will be to define patients who will benefit from the combination of hepatectomy to bile duct resection with lymphadenectomy and pancreatoduodenectomy.

Key words: liver tumors – cholangiocarcinoma – liver resection – biliary drainage

Introduction

Cholangiocarcinoma (CCC) is the second most common primary liver cancer, which may arise at any point in the biliary tree, from small intra-hepatic bile ducts to the common bile duct. The reported autopsy incidence of the CCC is estimated from 0.01 to 0.5% [1]. Most tumors occur in the age group of 50–70 years. A number of factors or disease have been implicated to the development of CCC. Primary sclerosing cholangitis is a major risk factor with an interval between the diagnosis of sclerosin cholangitis and CCC ranging from 1 to more than 25 years [2]. Other rare conditions associated with the development of CCC include ulcerative colitis, bile-duct adenoma, multiple biliary papillomatosis and pancreaticobiliary maljunctions [3]. All members of the congenital fibropolycystic family may be complicated by CCC, including congenital hepatic fibrosis, cystic dilatation (Caroli's syndrome), choledochal cyst, polycystic liver and Von Meyenburg complexes [4].

CCC can be divided into three principal types: intrahepatic, hilar and distal (Figure 1). The clinical feature and the treatments differ according to the type and site of the CCC. Intrahepatic cholangiocarcinoma are usually treated like primary liver tumors with hepatic resection. Hilar tumors involving the confluence of bile ducts are also called Klatskin tumors. They are the most frequent and present the greatest challenge in preoperative diagnosis and in the surgical management. Distal cholangiocarcinomas included tumors that involved pedicular and intrapancreatic portion of the bile duct. The definition of cholangiocarcinoma does not usually include cancers of the gallbladder and of the ampulla because of their different clinical course and prognosis.

Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma (ICCC) is a rare malignant epithelial tumors which originate in the intrahepatic bile ducts [5]. Such tumors are the second most common primary liver cancer after hepatocellular carcinoma and has only recently been identified as a separate entity with specific pathological and radiological features [6–8] (Figures 2–3). In recent years in the United States there has been a marked increase in the incidence of mortality from ICCC and this tumor continues to be associated with poor prognosis [9]. The majority of patients with ICCC have an underlying normal liver, although some underlying liver disease may favor the development of ICCC such as Caroli disease, sclerosing cholangitis, thorotrast deposition, parasitic infestation and hepatolithiasis [10–11]. ICCC according to the Liver Cancer Study Group of Japan classification was classified into three types based on the basis

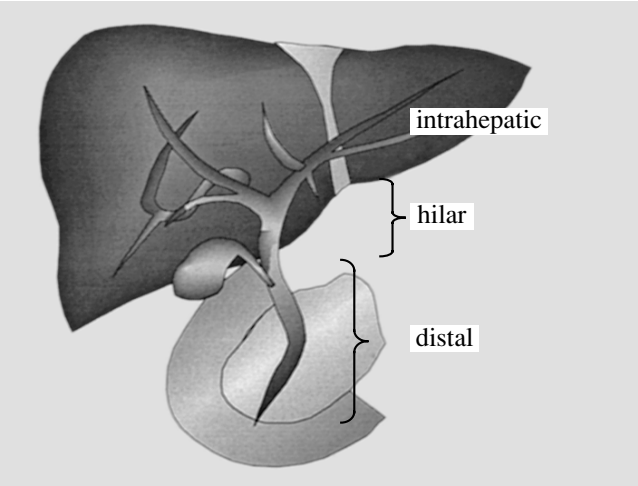

Fig. 1. Three principal types of CCC: intrahepatic, hilar and distal.
Рис. 1. Три основные типа ХК: внутрипеченочный, гилюсный и дистальный.

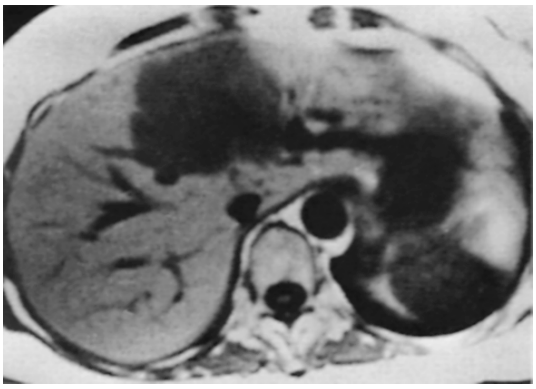

Fig. 2. Intrahepatic Cholangiocarcinoma: the most common type "mass forming" MRI T1.
Рис. 2. Внутрипеченочная холангиокарцинома: самый часто встречающийся – массивный тип – МРТ Т1.

Fig. 3. Intrahepatic Cholangiocarcinoma: the most common type "mass forming" gross pathological anatomy.
Рис. 3. Внутрипеченочная холангиокарцинома: самый часто встречающийся – массивный тип – макропрепарат.

of macroscopic appearance of the cut surface of the tumor: mass forming, which is the commonest type (Figure 4); periductal-infiltrating (Figure 5) and intraductal growth type (with papillary growth or forming a tumor thrombus) [12] (Figure 6–7). Owing to its intrahepatic location, the tumor rarely produces early symptoms and is discovered at an advanced stage [13]. Therefore, the presentation of ICCC is similar to other intrahepatic malignancy and includes abdominal pain and weight loss. Jaundice is rare and only occurs at a late stage with invasion of the hepatic confluence by tumor.

Imaging findings of mass forming type ICCC consist of a large fibrous non-encapsulated heterogeneous tumor often difficult to be differentiated from metastatic tumors. Pathologic examination of percutaneous tumor biopsies shows a mucosecreting adenocarcinoma with a great density of fibrosis. The periductal-infiltrating type of ICCC rapidly caused obstructive jaundice and is often difficult to differentiate preoperatively from a Klatskin tumor. However, the periductal-infiltrating type of ICCC is a relative large mass with hilar invasion after extension into the hepatic hilus from an intrahepatic segmental duct, whereas the former is a rather small tumor. Both mass forming and periductal-infiltrating types are associated with satellite nodules, focal liver atrophy, localized dilatation of intrahepatic bile ducts narrowing of portal adjacent veins and a retraction of the liver capsule [8–14]. Most intraductal growth type of ICCC does not show extraductal extension of the tumor and are limited to the rather large segmental bile duct wall. Histologically, the tumors are papillary adenocarcinoma and/or well-differentiated tubular adenocarcinoma with less frequent vascular, lymphatic and perineural involvement.

ICCC are generally discovered at an advanced stage and in some series only 30% of these patients have resectable tumors [15]. At the time of surgery, mean tumor size varies from 6 to 10 cm and often centrally located [13]. Most of these tumors could therefore only be removed through major hepatectomy including portal vein resection and reconstruction [16–18]. The high hilar lymph node invasion rate of ICCC requires an extensive hepatoduodenal lymphadenectomy [19]. The postoperative mortality rate ranges between 3 and 7% [17, 20, 21].

Despite of these extensive surgery, the 5-year overall survival rate varies from 25% to 50% [11, 13, 18–25]. These differences may be explained by differences in the gross anatomy of ICCC. Intraductal ICCC, which are rare in Western countries, have a better long-term prognosis, and mass forming type has a better prognosis than periductal-infiltrating type [24–29]. The worse prognosis of the periductal-infiltrating type is due to its spread along Glisson's capsule and the higher incidence of lymph node involvement [24].

The presence of satellite nodules, metastatic lymph nodes invasion, tumor size, and vascular invasion are the predominant prognostic factors [13, 20, 22, 24, 30]. A 5-year survival rate of patients without satellite nodules or positive lymph nodes can be observed in 35% of

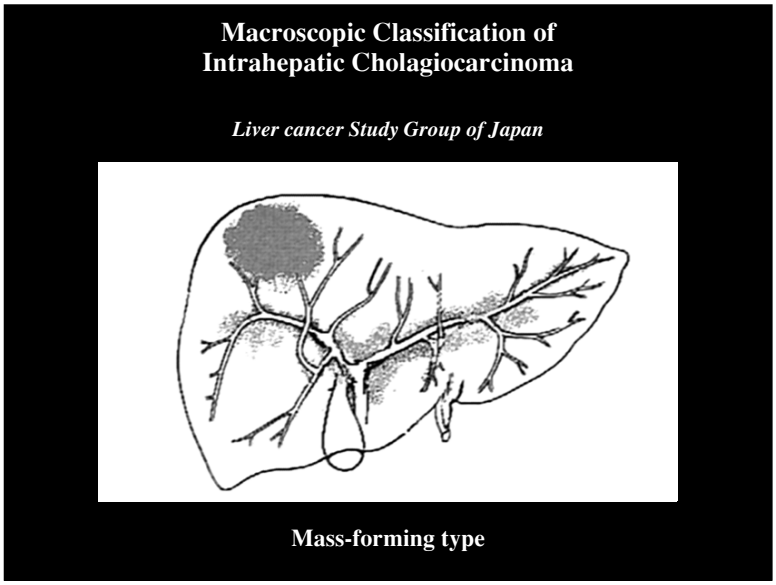

Fig. 4. ICCC according to the Liver Cancer Study Group: mass forming type.
Рис. 4. ВХК по классификации Группы по исследованию рака печени: массивный тип роста.

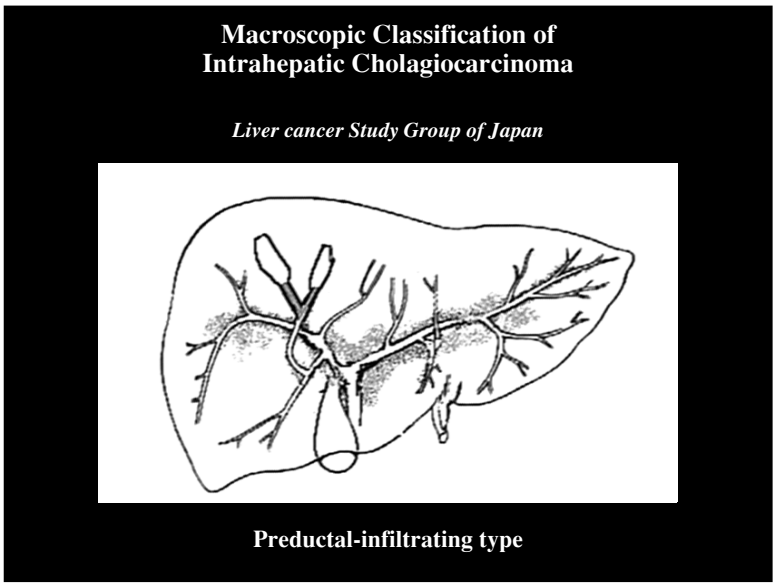

Fig. 5. ICCC according to the Liver Cancer Study Group: periductal-infiltrating type.
Рис. 5. ВХК по классификации Группы по исследованию рака печени: перипротоково-инфильтрирующий тип роста.

cases [17]. Few patients with one other features survived for more than 3 years [13, 15, 16, 20–23, 30]. Intrahepatic recurrences are the most common causes of death. These recurrences are not accessible to any form of treatment in contrast to hepatocellular carcinoma [31]. Liver transplantation is not an effective therapy for ICCC [32].

Hilar Cholangiocarcinoma

Hilar cholangiocarcinoma (HCCC), proximal bile duct tumor, carcinoma of the hepatic duct confluence and Klatskin tumor are all synonyms for the same tumor defined by Klatskin in 1965 as an adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatitis (Figure 8). According to their localization, HCCC are classified into four types. Type I tumors are localized below the biliary confluence, type II tumors reach the confluence, type III tumors reach the common hepatic duct into either the right (IIIa) or the left hepatic duct (IIIb), and type IV tumors are characterized by bilateral involvement of the biliary confluence into both right and left hepatic ducts. Despite of its slow growth and the seldom of distant metastases, the diagnosis of HCCC is usually lately made when the bile duct is occluded and the patient if jaundiced. The ma-

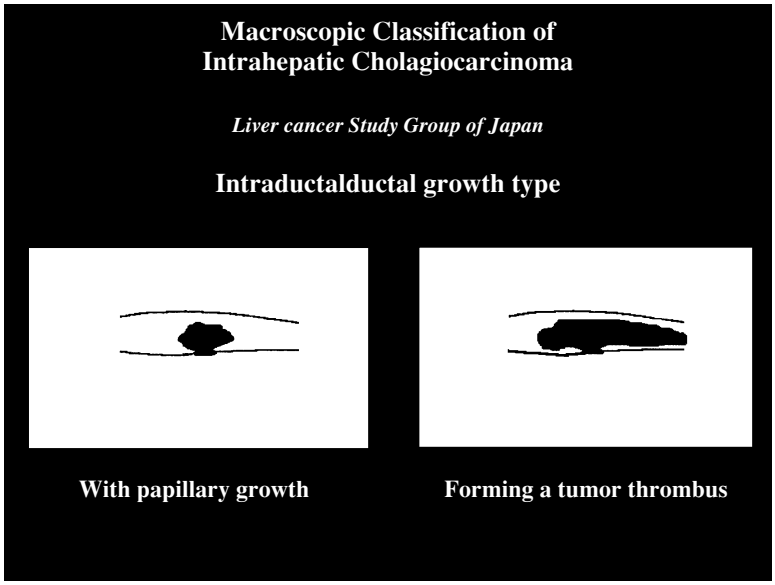

Fig. 6. ICCC according to the Liver Cancer Study Group: intraductal growth type.
Рис. 6. ВХК по классификации Группы по исследованию рака печени: внутрипротоковый тип роста.

jority of HCCC are small infiltrating tumors (Figure 9). They are difficult to manage surgically because of the involvement of the portal vein, the hepatic artery and/or the parenchyma of the liver around the hepatic hilum, including the caudate lobe. Although the papillary variant is uncommon, it has a higher resectability with a better long-term outcome, since this variety of carcinoma is seldom associated with vascular invasion and lymph nodes involvement [33, 34] (Figure 10). HCCC frequently spreads along the nerves and invades contiguous vascular structures [35]. In addition, many of these lesions will demonstrate both intraductal and periductal spread along the bile duct itself [36]. These characteristics make surgical resection often difficult and challenging. However, surgical resection remains the best treatment for HCCC because it increases the length and the quality of survival. Most of the controversy is about the extent of the resection in order to achieve a complete removal of the tumor [33]. Accurate preoperative staging, intraoperative assessment and pathological classification contribute to a rational approach of these challenging cases.

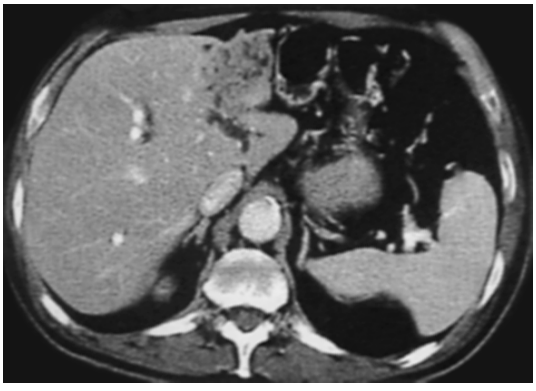

Fig. 7. ICCC: the "intraductal growth type" does not show extraductal extension and are limited to the rather large segmental bile duct wall.
Рис. 7. ВХК: внутрипротоковый тип роста, при котором нет распространения за пределы протока, опухоль ограничена стенкой довольно крупного сегментарного протока.

Jaundice is the most frequent symptom. Other symptoms include weight loss, abdominal pain, pruritus and fever. The purpose of preoperative investigations is to identify the level and the extent of the obstruction and any vascular involvement which can be indirectly supposed by the presence of an atrophy-hypertrophy complex. In very exceptional cases, benign localized biliary hilar stricture can mimic Klatskin tumor [37]. Ultrasonography and computed tomography (CT) can provide important information regarding the nature, the exact location of the bile duct dilatation, the size and the diameter of the mass, and its relationship to surrounding structures. CT is more sensitive than ultrasound for the detection of any tumor mass, lobar atrophy or the relationship between the caudate lobe and the tumor. ERCP often does not provide adequate visualization of the intrahepatic ducts near to the obstruction, and is associated with an increased risk of bacterial contamination [38]. Percutaneous transhepatic cholangiography (PTC) provides direct imaging of proximal bile ducts. It accurately defines the extension of the tumor proximally and may facilitate treatment with the placement of a biliary drainage [38]. The anatomic staging of patients according to the classification of Bismuth defines the possibilities of the resection for each type. The combination of cholangiography and percutaneous transhepatic cholangioscopy has been proposed as a more accurate mean of assessing spread along the bile duct [36]. Despite the fact that duplex sonography can correctly determine vascular patency

in 80% of cases [39], like many other authors we recommend hepatic arteriography and portal venography to complete the preoperative resectability [40]. Magnetic resonance imaging (MRI) permits excellent visualization of hepatic parenchymal abnormalities, as well as the visualization of the biliary tree and vascular structures. Because MRI is non-invasive and does not involve exposure to radiation, it may replace CT and angiography [2]. Although a promising imaging technique, endoscopic ultrasonography can't correctly explore the bile duct bifurcation.

Established criteria of non-resectability at the preoperative stage are: (a) bilateral intrahepatic bile duct involving left and right segmental branches; (b) bilateral involvement of hepatic arterial or portal venous branches and (c) a combination of unilateral hepatic arterial involvement with contralateral biliary spread [40, 41]. In our opinion, resectability which was classically assessed according to the Bismuth's classification should be reevaluated. It is notable that the type IV with diffuse bilateral duct involvement, long time considered as an absolute contraindication, was resectable in some cases [21]. Therefore there is a need of a classification including biliary, vascular and parenchymal extension.

When preoperative investigations clearly demonstrate non-resectability, some authors advocate bypass surgery to segment III duct of the left liver or to the anterior portal pedicle of the right liver [42–44]. Percutaneous stenting using large diameter metal stents contribute to increase long-term patency and therefore provide in our experience a good palliative procedure [44].

The goals of operative therapy for patients with HCCC include relief of the jaundice and, if possible, removal of the tumor. Although palliative resection may be accompanied by and excellent pain relief improving the patients quality of life, the survival and recurrence-free rate for patients with tumor-free surgical margins are better than those with involved surgical margins or residual macroscopic disease [33, 41]. Therefore, to obtain surgical curability, no microscopic residual tumor or invaded surgical margins should be found in postoperative histological examinations [12].

Tumors below the confluence of the hepatic ducts can be treated by local resection with subsequent biliary reconstruction. The perioperative mortality is less than 5% [24] and the 5-year survival rate for patients with negative microscopic margins is 20% [23, 45].

Tumors invading the confluence should be treated by hepatic resection including resection of the caudate lobe [45]. The necessity of combined resection of the caudate lobe was emphasized by Mizumoto et al. [46]. Many biliary tributaries of the caudate lobe originate directly from the confluence and thus allow for location of intrahepatic bile duct involvement [47]. This policy, initiated by Nimura [48], resulted in a dramatic increase of resectability from 15 to 80% over the last 10 years (Table 1). Overall, a 5-year survival rate for patients who underwent hepatic resection can be expected

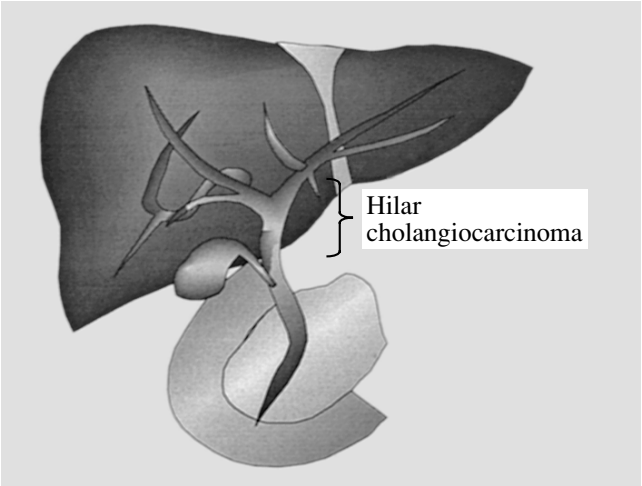

Fig. 8. Hilar cholangiocarcinomas (HCCC), proximal bile duct tumor, carcinoma of the hepatic duct confluence and Klatskin tumor are all synonyms for the same tumor defined by Klatskin in 1965 as an adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatitis.
Рис. 8. Гилюсная холангиокарцинома (ГХК), опухоль проксимальных желчных протоков, рак конфлюенса печеночных протоков и опухоль Клатскина – это синонимы одной и той же опухоли, которую в 1965 г. Клатскин определил как аденокарциному общего печеночного протока, развившуюся в месте его бифуркации в воротах печени.

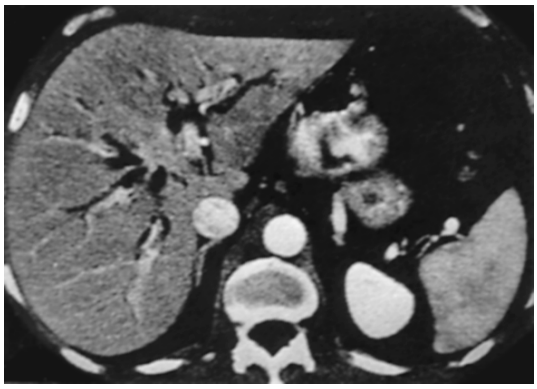

Fig. 9. The majority of HCCC are small infiltrating tumors.
Рис. 9. Большинство ГХК – небольшие инфильтрирующие опухоли.

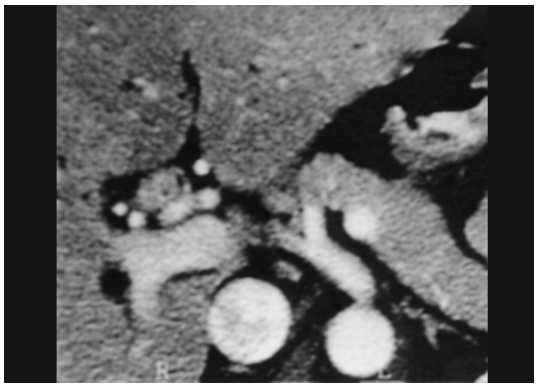

Fig. 10. Papillary variant of HCCC.
Рис. 10. Папиллярный вариант ГХК.

Table 1. Results of surgery for hilar cholangiocarcinoma

Authors	Year	Resectability rate (%)	Major hepatectomy *N*	Mortality rate (%)	5 Year survival (%)	Median survival (months)
Bismuth[49]	1992	19	13	0	–	24
Pichlmayr[50]	1996	45	111	9.9	28.4	24
Kempnauer[51]	1997	50	111	9.9	28.4	24
Miyazaki[52]	1998	63	53	15	26	–
Nimura[48]	1998	80	109	9.7	25.8	–
Kosuge[53]	1999	61	52	9.2	32.8	28
Gerhard[54]	2000	–	32	18	–	–
Beaujon	1998	59	27	11	–	28

in 25%, with a 30% of 5-year survival rate in patients with negative microscopic margins [33, 45, 48].

Hepatic resection increases the survival, but is associated with a high postoperative mortality rate around 10% (Table 1) [48–54]. Liver resection in patients with severe obstructive jaundice and cholangitis is associated with severe complications, including intraoperative bleeding, postoperative subphrenic abscesses due to biliary fistula and liver failure [55]. Several studies have focused on the preoperative clearance of jaundice and cholangitis [55]. Although prospective randomized controlled trials has failed to demonstrate a reduction of mortality or morbidity, we as well as others authors advocate preoperative percutaneous transhepatic biliary drainage (PTBD) [38, 56]. The main advantage of PTBD is firstly to control localized cholangitis, and secondly to provide an accurate diagnosis and staging of the extent of carcinoma. It allows designing a precise operative procedure for each patient prior to surgery [38]. PTBD allows the use of percutaneous transhepatic portal vein embolization in order to increase the volume of the remnant liver, preventing post-hepatectomy liver failure [57–61]. As shown in Table 2, the increase use of PTBD at Beaujon Hospital was associated with an increase of more complex resections, including vascular reconstruction. Furthermore, complications of PTBD decreased while our experience of this procedure increased. Along with a better staging of HCCC using selective cholangiography, angiography and preoperative portal embolization there is a trend to preserve the uninvolved liver parenchyma by performing a resection of the caudate lobe together with the smallest necessary resection of the involved segment [57]. Portal vein involvement by HCCC is usually a contraindication to resection but segmental portal vein invasion of the tumor can be excised and the portal vein reconstructed, resulting in a better long-term survival than palliative procedure alone [62–64].

Table 2. Beaujon's Hospital experience with preoperative percutaneous transhepatic biliary drainage (PTBD) before major liver resection for hilar cholangiocarcinoma

Procedures or complications of PTBD	1992–1995	1995–2001
More than 4 weeks drainage (%)	50	80
More than 2 drains (%)	30	70
Hemobilia (%)	20	5
Infectious complications (%)	60	25

Adjuvant therapy includes radiation therapy and chemotherapy. Radiation therapy can be given intraoperatively or postoperatively as an external beam radiation or as endoluminal brachytherapy. Some data show that in some patients with microscopically involved margins, adjunctive radiotherapy in combination with Fluorouracil, survival appears to be prolonged chemotherapy improve results [65, 66].

Results of liver transplantation in patients with nonresectable HCCC or lymph node involvement have been disappointing with a 5-year survival rate of less than 20% [67]. It seems therefore that whatever the resectability and the location of the tumor, HCCC should not be considered longer as an indication for liver transplantation [68, 69]. However, a prolonged tumor-free survival can be obtained in very selected patients with primary sclerosing cholangitis with CCC, liver transplantation associated with preoperative external-beam and internal transcatheter radiation and continuous intravenous chemotherapy [2].

Distal Cholangiocarcinoma

According to their location, tumors of the common bile duct are usually subdivided into middle (or pedicular) and distal (or intrapancreatic) subgroups (Figure 11). However, as the middle lesions are often associated to lymph node and perineural invasion often requiring pancreaticoduodenectomy (PD) [70]. Therefore we include all CCC developing below the confluence in the distal group.

The main clinical symptom observed in distal cholangiocarcinoma (DCCC) is jaundice. Other symptoms include weight loss, abdominal pain, pruritus and fever.

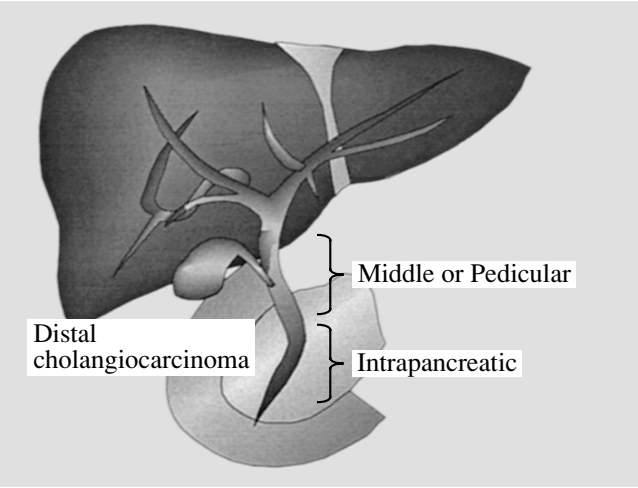

Fig. 11. Distal Cholangiocarcinomas are subdivided into middle (or pedicular) and distal (or intrapancreatic) subgroups.
Рис. 11. Дистальную холангиокарциному (ДХК) делят на срединную (или педикулярную) и дистальную (или интрапанкреатическую) подгруппы.

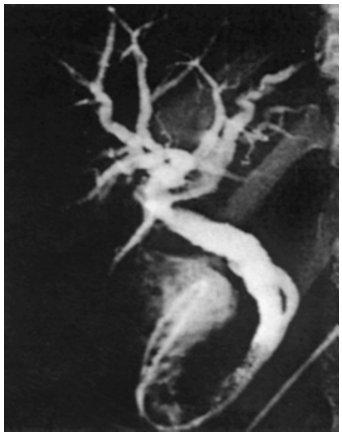

Fig. 12. One case of benign stricture of the distal portion of the common bile duct can mimic malignant tumor.
Рис. 12. Доброкачественная стриктура дистальной части общего желчного протока, имитирующая злокачественную опухоль.

Diagnostic investigations suggested the correct final diagnosis in less than 50% of cases [71]. Some cases of benign strictures of the pedicular portion of the common bile duct can mimic DCCC. These benign strictures include benign tumors such as papilloma, adenomyoma, fibroma and granular cell tumor [4] or other cases of localized sclerosing cholangitis and non-traumatic inflammatory strictures [4, 72] (Figure 12). Most tumors arising in the intrapancreatic portion of the common bile duct can grow up and was detected by US and CT as a mass in the periampullary region usually imputed to a pancreatic tumor. A rare but useful finding can be the thickening of the bile duct wall [71]. Echoendoscopy, which failed to localize and evaluate the extension of HCCC, has a high accuracy in the detection of DCCC [73]. The association of bile duct brush cytology to ERCP has a high sensitivity [74].

Approximately half of DCCC located in the pedicular portion of the common bile duct can be resected by extrahepatic bile duct resection, while all DCCC located in the intrapancreatic portion require a pancreaticoduodenectomy (PD). Few reports concerning the pathological extension of DCCC localized in the pedicular portion of the common bile duct have been published. However from our experience and according to others series a high proportion of patients with DCCC localized in the pedicular portion treated by extrahepatic bile duct resection had lymph node involvement in two thirds of cases, perineural invasion in 80% of cases and microscopic positive surgical margins, including pancreatic invasion in around 30% of cases [70, 75]. Therefore there are strong arguments in favor of PD in all DCCC, including those which are not localized in the intrapancreatic portion of the bile duct. Those arguments are, firstly, the lymphatic pathway of DCCC localized in the pedicular portion of the common bile duct included the superior border of the pancreas and retropancreatic area [70]; and secondly, postoperative mortality of PD has dramatically decreased in the 1990s toward zero [24].

The prognosis of patients with DCCC is significantly associated with pancreatic invasion, lymph node involvement, perineural and vascular invasion [76], with a 5-year survival rate from 28–53% [15, 23, 77]. After PD, survival of patients with DCCC and pancreatic invasion is similar to those with adenocarcinoma of the pancreas [78, 79].

Conclusion

Resection represents the only curative treatment for any type of CCC. Better selection of patients including the practice of invasive diagnostic procedure such as angiography, MRI, preoperative percutaneous transhepatic biliary drainage and preoperative portal vein embolization has led to increase the rate of the resectability with a 5 year survival rate in some cases of more than 30%. For unresectable cases, percutaneous or endoscopic stenting should be preferred to surgical palliative bypass procedure. Although the extent of resection remains controversial, progress in survival in patients with hilar cholangiocarcinoma was obtained by combining the hepatic resection including the removal of caudate lobe associated in some cases to portal vein reconstruction to the bile duct resection with large lymphadenectomy. In patients with DCCC, the progress may be obtained by combining the bile duct resection with pancreatoduodenectomy realizing a complete lymphadenectomy. Also the challenge will be to define patients who will benefit from the combination of hepatectemy to bile duct resection with lymphadenectomy and pancreatoduodenectomy.

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