REVIEW

Advances in diagnosis, treatment and palliation of cholangiocarcinoma: 1990-2009

Murad Aljiffry, Mark J Walsh, Michele Molinari

Murad Aljiffry, Mark J Walsh, Michele Molinari, Department of Surgery, Queen Elizabeth II Health Science Centre, Dalhousie University, Rm 6-254, Victoria Building, 1278 Tower Road, Halifax, Nova Scotia, B3H 2Y9, Canada
Author contributions: Aljiffry M and Molinari M contributed equally to this work by performing the literature search and by writing the paper; Walsh MJ reviewed and edited the manuscript.
Correspondence to: Michele Molinari, MD, Department of Surgery, Queen Elizabeth II Health Science Centre, Dalhousie University, Rm 6-254, Victoria Building, 1278 Tower Road, Halifax, Nova Scotia, B3H 2Y9,
Canada. michele.molinari@cdha.nshealth.ca
Telephone: +1-902-4737624 Fax: +1-902-4737639
Received: August 5, 2008   Revised: July 15, 2009
Accepted: July 22, 2009
Published online: September 14, 2009

Abstract

Several advances in diagnosis, treatment and palliation of cholangiocarcinoma (CC) have occurred in the last decades. A multidisciplinary approach to this disease is therefore recommended. CC is a relatively rare tumor and the main risk factors are: chronic inflammation, genetic predisposition and congenital abnormalities of the biliary tree. While the incidence of intra-hepatic CC is increasing, the incidence of extra-hepatic CC is trending down. The only curative treatment for CC is surgical resection with negative margins. Liver transplantation has been proposed only for selected patients with hilar CC that cannot be resected who have no metastatic disease after a period of neoadjuvant chemo-radiation therapy. Magnetic resonance imaging/magnetic resonance cholangiopancreatography, positron emission tomography scan, endoscopic ultrasound and computed tomography scans are the most frequently used modalities for diagnosis and tumor staging. Adjuvant therapy, palliative chemotherapy and radiotherapy have been relatively ineffective for inoperable CC. For most of these patients biliary stenting provides effective palliation. Photodynamic therapy is an emerging palliative treatment that seems to provide pain relief, improve biliary patency and increase survival. The clinical utility of other emerging therapies such as transarterial chemoembolization, hepatic arterial chemoinfusion and high intensity intraductal ultrasound needs further study.

INTRODUCTION

Cholangiocarcinomas (CC) are malignant tumors originating from epithelial cells lining the biliary tree and gallbladder[1]. Intrahepatic CCs (ICC) arise within the liver and extra-hepatic CCs (ECC) originate in the bile duct along the hepato-duodenal ligament. ICCs usually present as masses in the liver while jaundice is the most common presentation of ECCs. CCs are relatively rare tumors although their incidence is rising worldwide[2,3]. Several advances in the diagnosis, therapy and palliation of patients affected by CC have occurred during the last decades. The aim of this article is to review the most recent high quality literature on this topic.

EVIDENCE ACQUISITION

We sought studies that reported at least one of the following aspects of CC: epidemiology, diagnosis, therapy (e.g. surgery, radiotherapy, chemotherapy, phototherapy), and palliation. Preference was given to randomized controlled trials (RCT) and prospective observational studies. For each of these topics we searched MEDLINE, Ovid MEDLINE In-Process, Cochrane Database of Systematic Reviews, Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, EMBASE, PubMed, National Library of Medicine Gateway by established systematic review methods (Jadad Scale for RCT controlled studies, Downs and Black checklist for observational studies[4-6]. We further reviewed reference lists and articles from the authors' libraries. We limited our search to English-language articles published from January 1990 to June 2009. We then developed a comprehensive

Table 1 Summary of the terms used singly or in combination for evidence acquisition		
Primary MeSH terms	**Secondary MeSH terms (Epidemiology, diagnosis)**	**Secondary MeSH terms (treatment, palliation)**
Cholangiocarcinoma(s)	Epidemiology	Hepatectomy
Adenocarcinoma(s)	Classification	Resection
Carcinoma(s)	Diagnosis	Therapeutic(s)
Bile duct neoplasm(s)	Differential diagnosis	Treatment outcome(s)
Biliary tract neoplasm(s)	Early diagnosis	Surgery
Common bile duct neoplasm(s)	Risk factor(s)	Transplantation
Liver neoplasm(s)	Diagnostic imaging	Biliary tract
Bile duct(s)	Magnetic resonance imaging	Surgical procedures
Common bile duct	Endosonography	Liver transplantation
Intrahepatic bile duct(s)	Ultrasonography	Organ transplantation
Extrahepatic bile duct(s)	Emission computed tomography	Clinical trial
Biliary tract disease(s)	Radionuclide imaging	Controlled clinical trial(s)
Bile duct disease(s)	Positron emission tomography	Randomized controlled trial(s)
	X-ray	Clinical trial (phase I)
	Computed tomography	Clinical trial (phase II)
	Biopsy (needle)	Clinical trial (phase III)
	Biopsy (fine needle)	Clinical trial (phase IV)
	Cytology	Drug therapy
	Cytodiagnosis	Chemotherapy
	Tumor markers (biological) antigen(s)	Adjuvant
	Carcinoembryonic antigen	Antineoplastic agent(s)
	Ca 19-9 antigen	Combined modality therapy
	Ca 125 antigen	Antineoplastic
	Endoscopic retrograde cholangiopancreatography	Combined chemotherapy protocols
	Cholangiography	Neoadjuvant therapy
	In situ hybridization	Radiotherapy
	Fluorescence *in situ* hybridization	Adjuvant embolization
	Nucleic acid hybridization	Portal vein embolization
	Computed assisted image processing	Drainage
		Cholestasis
		Obstructive jaundice

and current database to catalog the medical literature on CC. The evidence database for the catalog was assembled only for CC arising in the intra- and extra-hepatic bile ducts. Our review did not include the management of gallbladder cancer, as several other comprehensive articles had already covered this topic[7-10]. To identify all potential papers, we searched medical subject headings reported in Table 1. Two authors (Aljiffry M and Molinari M) independently performed the selection of the articles based on the content of titles and abstracts. When in doubt, each article was reviewed entirely. The decision to include articles in this review was reached by consensus. For conciseness, a full list of search strategies, search results, and quality assessment for each included study are available on request from the corresponding author.

EPIDEMIOLOGY

The incidence of CC is rising in most countries and it is the second most common primary malignancy of the liver after hepatocellular carcinoma[1]. In the USA, approximately 5000 new cases are diagnosed every year[11] accounting for almost 3% of all tumors of the gastrointestinal tract[12]. While the incidence of ICC is rising, the occurrence of ECC is trending down[13,14] suggesting that different risk factors may be involved[15]. Caution should be used when interpreting these results as misclassification bias may have influenced these observations[2,16]. In fact, analysis of the Surveillance Epidemiology and End Results database from 1975 until

1999 has shown that most hilar tumors (more than 90%) were classified as ICC[2,16] while ECC were often combined with gallbladder cancers[2,13]. Nevertheless, evidence that ICC and ECC may be dissimilar tumors is supported by the recent discovery that, *in vitro*, they express diverse cellular proteins and have different cellular shape, doubling time, chromosome karyotype and chemosensitivity[17]. Similarly, researchers from France showed that hilar CC (HCC) express higher levels of MUC5AC (60% *vs* 22%), Akt2 (64% *vs* 36%), CK8 (98% *vs* 82%), annexin (56% *vs* 44%) and less vascular epithelial growth factor (22% *vs* 78%) in comparison to ICC[18]. These findings support the hypothesis that the heterogeneous protein and receptor expression of ECC and ICC may be due to different carcinogenic pathways[17,18].

ICC

The estimated age-adjusted incidence rates of ICC in the USA has increased by 165% over the last thirty years (from 0.32 per 100 000 in 1975-1979 to 0.85 per 100 000 in 1995-1999[2,19] accounting for 10% to 15% of all primary hepatic cancers[20]. The average age at presentation is the seventh decade of life[2] with a male to female ratio of 1.5[20]. The mortality rate and incidence of ICC have parallel trends[13] as age-adjusted mortality rate increased from 0.07 per 100 000 in 1973 to 0.69 per 100 000 in 1997[21].

ECC

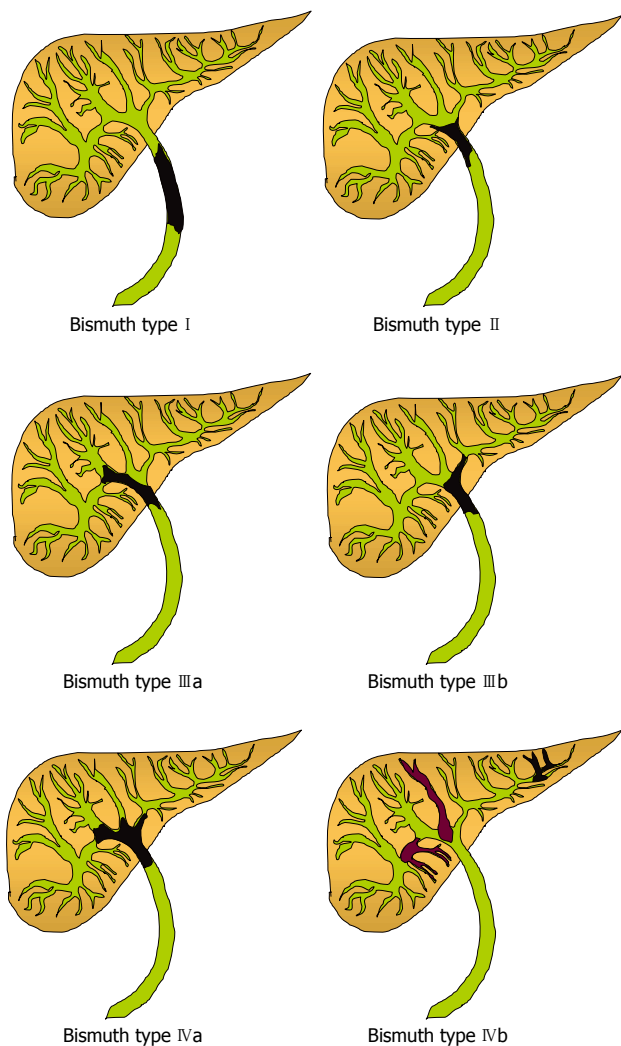In the USA, the age-adjusted incidence of ECC has

Figure 1 **Bismuth's classification of cholangiocarcinomas.** Type I: Cholangiocarcinoma is confined to the common hepatic duct; Type II: Cholangiocarcinoma involves the common hepatic duct bifurcation; Type IIIa: Cholangiocarcinoma affects the hepatic duct bifurcation and the right hepatic duct; Type IIIb: Cholangiocarcinoma affects the hepatic duct bifurcation and the left hepatic duct; Type IV: Cholangiocarcinoma is either located at the biliary confluence with both the right and left hepatic ducts involvement or has multifocal distribution.

decreased by 14% compared to data from two decades earlier. Currently it is 1.2 per 100 000 in men and 0.8 per 100 000 in women[2,22]. Similarly to ICC, 65% of ECC present in the seventh decade of life[22]. The mortality rate of ECC parallels its incidence and in the USA, the age-adjusted mortality rates for ECC declined from 0.6 per 100 000 in 1979 to 0.3 per 100 000 in 1998[14,21].

CLASSIFICATION

Anatomical classification

ICCs arise within the liver parenchyma while ECCs involve the biliary tree within the hepatoduodenal ligament and gallbladder. ECCs are further divided into hilar or distal tumors. HCC, also called Klatskin tumors, are located within 2 cm from the bifurcation of the common duct and were described for the first time by Klatskin in 1965[22]. Ten years later, Bismuth and Corlette proposed
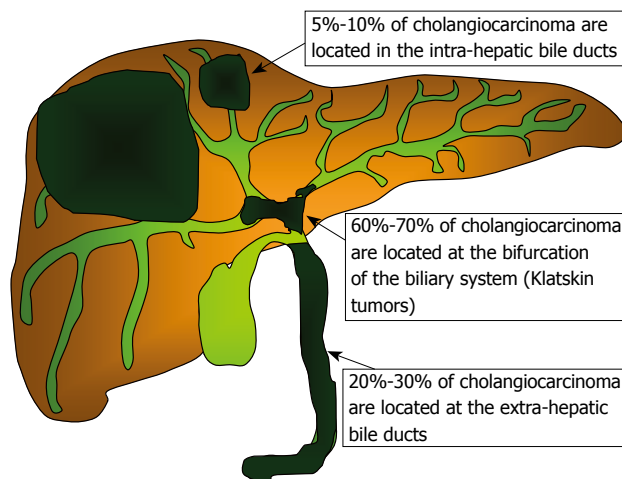

Figure 2 **Anatomical presentation of cholangiocarcinomas.** The majority of cholangiocarcinomas (60%-70%) present in the area of the biliary duct bifurcation and are called Klatskin tumors. The extra-hepatic bile duct is involved in 20%-30% of cases while intrahepatic cholangiocarcinomas represent 5%-10% of the tumors originating from the biliary system.

a clinical classification that stratifies these tumors by anatomical location (Figure 1)[23]. Approximately 60% to 70% of CC are located in the hylum, 20% to 30% are ECC, and 5% to 10% are ICC (Figure 2)[24,25].

Pathological classification

More than 90% of CC are well- to moderately-differentiated adenocarcinomas[26,27] with tendency to develop desmoplastic reaction and early perineural invasion. Macroscopically, ICC may develop in solid masses, infiltrate periductal tissues, grow intraductally or have mixed characteristics. On the other hand, ECC develop nodular lesions, sclerosing strictures, or papillary growth patterns. Sclerosing CC are the most common[28] while papillary adenocarcinomas are rare and associated with more favorable prognosis[22].

RISK FACTORS FOR CHOLANGIOCARCINOMA

Only a minority of patients presenting with CC have known risk factors such as chronic biliary inflammation, cholestasis or congenital abnormalities (Table 2)[29].

Primary sclerosing cholangitis (PSC)

In Western countries, PSC is the most important predisposing factor for CC[30,31]. The cumulative annual risk of CC in patients with PSC is 1.5% per year after the development of jaundice[32] and the prevalence of CC in patients with PSC ranges between 8% and 40%[30,33,34]. A recent epidemiological study from the Netherlands has shown that the risk of CC for patients with PSC is 9% after 10 years from the time of the diagnosis[35]. In patients with concomitant inflammatory bowel disease, the 10-year and 20-year risks for CC are 14% and 31% respectively, which are significantly higher than patients without inflammatory bowel disease (2% and 2%

Table 2 Known risk factors for cholangiocarcinomas
General risk factors
Old age (older than 65 years)
Smoking
Obesity
Diabetes
Post surgical
Biliary-enteric anastomosis
Chronic inflammatory diseases
Primary sclerosing cholangitis (PSC)
Hepatolithiasis (Oriental Cholangiohepatitis)
Hepatitis C
Hepatitis B
Human Immunodeficiency Virus (HIV)
Liver cirrhosis
Parasitic infections
Opisthorchis viverrini
Clonorchis sinensis
Congenital
Choledochal cysts
Caroli's disease
Congenital hepatic fibrosis
Chemical agents
Thorotrast
Dioxin
Nitrosamines
Asbestos
Medications
Oral Contraceptive Pills
Isoniazid

respectively; $P = 0.008$[35]. Individuals with PSC frequently develop CC at younger age (30-50 years) compared to the general population (60-70 years)[30,32]. The diagnosis of CC in this group is challenging because clinical presentation and radiological findings of CC and PSC are similar. As a result, most cases of CC complicating PSC are detected at advanced stages and have poor prognosis[36]. Predictive factors of CC in PSC patients are: sudden progressive jaundice, unintentional weight loss, marked dilation of bile ducts proximal to biliary strictures, serum level of Ca 19-9 tumor marker above 100 U/mL, and presence of cellular dysplasia on cytological specimens obtained by brushing of the biliary ducts[37].

Parasitic infections
Infestation with liver flukes (*Opisthorchis viverrini* and *Clonorchis sinensis*) has been strongly associated with an increased risk of CC in South-East Asia[3,38,39]. In areas where *Opisthorchis viverrini* is endemic, the adjusted prevalence for CC by age and gender is as high as 14%[40]. The pathophysiology causing CC in these patients is not completely understood, however it is hypothesized that parasites colonize the biliary system causing chronic inflammation and predisposing to malignant transformation.

Intrahepatic biliary stones (Hepatolithiasis)
Oriental cholangiohepatitis (also known as recurrent pyogenic cholangiohepatitis) has a prevalence of 20% in South-East Asia[41] and almost 10% of affected patients develop ICC[42-45]. Recurrent episodes of cholangitis aggravate the chronic inflammatory process that persists

between flare ups. Risk factors associated with CC in these patients are: age over 40 years, long history of hepatolithiasis, unintentional weight loss, increasing serum alkaline phosphatase, decreasing serum albumin, and serum CEA tumor marker above 4.2 ng/mL[46].

Congenital biliary cystic diseases
Patients with choledochal cysts have low risk for CC if the cyst is excised early in their life[46]. On the other hand, the incidence of malignant degeneration is between 10% and 20% if the cyst is not excised by the age of 20 years[28,47]. The mechanism of malignant transformation is not totally understood although biliary stasis and reflux of pancreatic secretions are suspected of causing neoplasia through chronic inflammation[48]. CC can occur years after resection of the cyst suggesting that there might be a genetic defect predisposing to tumors of the biliary system[49].

Liver cirrhosis and viral infections
The risk of developing CC in cirrhotic patients is ten-fold higher than the general population (0.7% *vs* 10.7%)[2,50]. Among patients with CC in the USA, the prevalence of hepatitis C viral infection (HCV) was found to be four times higher than the general population (0.8% *vs* 0.2%)[20]. These results have been confirmed in Italy[51], in Taiwan[52] and in Japan where HCV and viral hepatitis B (HBV) infection were detected in 23% and 11.5% of CC compared to 6% and 5.5% of controls, respectively, with cumulative rates 1000-times greater than the general population[53]. Similar results were recently confirmed in a case-control study performed in China, where researchers found that at multivariate analysis, significant risk factors for the development of ICC were hepatolithiasis (adjusted OR: 5.7; 95% CI: 1.9-16.8) and HBV infection (adjusted OR: 8.8; 95% CI: 5.9-13.1)[15]. A large epidemiological study from the United States validated that HCV infection is a risk factor for ICC (hazard ratio 2.55; 95% CI: 1.3-4.9) but not for ECC (hazard ratio 1.5; 95% CI: 0.6-1.85)[54]. Although human immunodeficiency virus (HIV) does not cause cirrhosis *per se*, 0.5% of patients infected with HIV have been found to have CC in comparison to 0.1% among controls, confirming previous observations which suggested that chronic viral infections might predispose to neoplastic transformation of some cell lines[20].

Chemical agents
Several compounds have been suspected of causing CC. Thorotrast (thorium dioxide) needs a special mention because it was used as a radiological contrast in the period between 1920-1950 and was found to increase the risk of CC up to 300-times in comparison to the general population[16,55]. Because of its long biological half-life (400 years), the latency period of thorotrast-induced CC ranges between 16 to 45 years[56], with the highest incidence between 20 to 30 years after exposure[57]. A few studies have shown an association between CC and other chemical agents such as asbestos[58], vinyl chloride[59] and nitrosamines[60]. Medications such as isoniazide[61] and first generation of oral contraceptives[62] are also suspected of increasing the risk of CC.

Other risk factors

Tobacco smoking is weakly associated with CC in the general population[20] while it appears to be a strong risk factor for PSC patients[63]. Other predisposing factors for CC are diabetes, obesity, presence of bile duct adenomas and biliary papillomatosis[64,65]. Although there is no evidence that endoscopic sphincterotomy increases the risk of CC, biliary-enteric bypasses may do so[66].

DIAGNOSIS

Clinical presentation

CCs are usually clinically silent or associated with nonspecific symptoms in early stage (Table 3)[67,68]. ICCs are often diagnosed by imaging tests, and rarely during physical exams, as asymptomatic hepatic masses[26]. On the other hand, ECC usually present with painless jaundice[69] and symptoms related to biliary obstruction such as itching, clay-colored stool and hyperpigmented urine[69]. Only 10% of cases present with ascending cholangitis[70]. Jaundice is usually persistent and progressive while intermittent biliary obstruction may be observed in patients with papillary lesions that cause a ball-valve effect[71]. Physical examination of patients with CC may reveal hepatomegaly, palpable gallbladder (Courvoisier sign), or signs of portal hypertension due to portal vein thrombosis secondary to tumor invasion or compression[33,69].

Laboratory investigations

Serum biochemical tests usually support the clinical suspicion of CC but they are rarely diagnostic. Jaundice occurs only if there is obstruction of the two main intra-hepatic biliary ducts or common bile duct. In these circumstances, elevation of the serum levels of bilirubin and markers of biliary epithelial injury, such as alkaline phosphatase (ALP) and gamma glutamyltransferase (GTT)[33], are common[72,73]. On the other hand, in the presence of unilateral intrahepatic biliary obstruction, elevation of ALP or GTT may be present without increase in the serum bilirubin level[33]. Other abnormal laboratory findings include hypoalbuminemia and prolonged prothrombin time, which reflect the combination of diminished hepatic synthetic function, cachexia and malabsorption of vitamin K[33].

Serum tumor markers

Several tumor markers may support the diagnosis of CC, although none of them is sensitive enough to be used for screening purposes. The most commonly used markers are carbohydrate antigen (Ca 19-9) and carcinoembryonic antigen (CEA)[73]. These tumor markers are not very specific as they can be elevated in the presence of other malignancies (e.g. pancreas and stomach) and with benign conditions such as cholangitis and hepatolithiasis[73-75]. In patients without PSC, serum Ca 19-9 values above 100 U/mL have a sensitivity of 53% and specificity of 75%-90% for the diagnosis of CC[74]. In patients with PSC, serum Ca 19-9 levels above 100 U/mL have sensitivity of 75%-89% and specificity of 80%-86% for the diagnosis

Table 3 Presenting symptoms of patients affected by cholangiocarcinomas	
Symptoms	Percentage (%)
Jaundice	84
Weight loss	35
Abdominal pain	30
Nausea and vomiting	20
Fever	10

of CC[75-77]. In a recent study from the Mayo Clinic, the optimal cutoff value for serum Ca 19-9 in patients with PSC was 20 U/mL which provided a sensitivity of 78%, specificity of 67%, positive predictive values of 23% and negative predictive value of 96%[78]. Serum Ca 19-9 combined with either ultrasonography, computed tomography, or magnetic resonance imaging provided a sensitivity of 91%, 100% and 96% respectively for CC diagnosis[78]. The levels of Ca 19-9 seem to correlate with the stage of the disease. Patel et al[72] reported that the sensitivity of Ca 19-9 above 100 U/mL for the diagnosis of CC in patients with resectable tumors was 33% compared to 72% in patients with unresectable tumors. Using more than one tumor marker for patients with PSC may improve the detection rate of CC. In one study, using Ca 19-9 levels above 180 U/mL in combination with CEA levels above 5.2 ng/mL had a sensitivity of 100% and a specificity of 78.4%[79]. Several new markers are currently being investigated. The human mucin 5, subtypes A and C (MUC5AC) are the most promising for future clinical use with sensitivity and specificity of 71% and 90%, respectively[80].

Imaging modalities

Imaging modalities are essential for the diagnosis and treatment planning of patients with CC[73].

Abdominal ultrasound (US)

US is usually the initial imaging test performed to evaluate patients with biliary obstruction[81]. The sensitivity and accuracy of US for ECC diagnosis are 89%[82] and 80%-95%, respectively[83,84]. On the other hand, ICC are difficult to distinguish from other solid intra-hepatic masses as they lack specific US features[83,84]. The use of duplex US with color Doppler technology is helpful in assessing portal venous invasion and hepatic parenchymal involvement. In a small series of patients with HCC, duplex US detected portal vein invasion correctly in 86% of patients[85]. In a larger study, duplex US was 93% sensitive and 99% specific for detecting portal vein involvement[86]. As the sensitivity and specificity of US are operator-dependent, most patients with suspected CC undergo further imaging modalities to confirm and stage suspected tumors[87]. The sensitivity of US improves significantly in the presence of elevated serum tumor marker Ca 19-9[80]. Serum level of Ca 19-9 above 20 U/mL in patients with PSC has been shown to increase the diagnostic sensitivity of abdominal US up to 91%, with specificity of 62%, positive predictive value of 23%, and negative predictive value of 98%[80].

Computed tomography (CT)

Triple-phase CT scan is widely used to diagnose and stage CC[88] as it provides valuable information regarding local spread, vascular invasion, lymph node involvement and presence of distant metastases[89,90]. On CT scans, ICC usually present as hypodense lesions with irregular margins on initial images and a variable degree of delayed venous phase enhancement[86]. These characteristics have been shown to correlate with prognosis as hyperattenuating CC have a more aggressive behavior[91]. Other CT findings of ICC include dilatation and thickening of the peripheral intra-hepatic bile ducts and liver capsular retraction[92]. ECC may be seen as a focal thickening of the ductal wall with various enhancement patterns[93]. However, in many cases of ECC, visualization of the neoplasms is not definitive because they are too small to be detected. More recent studies[92,94] have shown that modern contrast-enhanced multidetector row computed tomography was 78.6%-92.3% accurate for the diagnosis of ECC, although there was a strong tendency to underestimate the longitudinal extension of the tumor (77.8%) in comparison with the pathological results of the excised specimens[95,96]. Four-channel multidetector-row CT has been shown to correctly diagnose hepatic artery invasion with 100% sensitivity and 90% specificity and portal vein invasion with 92.3% sensitivity and 90.2% specificity[96]. Regular enhanced CT can be extremely useful by showing indirect signs of ECC such as biliary ductal dilatation and hepatic lobar atrophy. Atrophy of one hepatic lobe could be associated with hypertrophy of the opposite lobe, a condition known as the atrophy-hypertrophy complex. This phenomenon is seen when CC obstruct the biliary outflow of a single lobe and invade the ipsilateral portal vein causing compensatory hypertrophy of the opposite hepatic lobe[97]. The sensitivity of triple-phase helical CT in the detection of HCC is in the range of 90% to 100%[92,98] and it is even more sensitive in detecting ICC greater than 1 cm in size[90]. These results show a marked improvement in the diagnostic yield of CT compared to previous reports in which the tumor detection rate was only 60%[99]. CT is also useful for assessing the vascular and lymph node status of patients affected by CC. In a series of 55 patients with HCC, CT accurately predicted portal vein invasion, arterial invasion, and lymph node involvement in 86%, 93%, and 84% of patients, respectively[100]. The overall accuracy of CT for determining resectability of CC is in the range of 60% to 85%[90,100,101]. Recently, CT cholangiography (CTC) has been shown to be a promising modality for delineating the biliary tree. In a large study, CTC was superior to conventional CT or US and equal to endoscopic retrograde cholangiopancreatico graphy (ERCP) for the diagnosis of HCC[102]. In another smaller study, the sensitivity and specificity of CTC for malignant biliary obstruction were both 94%[103]. One of the limitations of CTC is that optimal imaging quality depends on the secretory function of the liver[104]. For patients affected by PSC, the combination of tumor serology (serum level of Ca 19-9 above 20 U/mL) and contrast-enhanced abdominal CT scan has been shown to improve the diagnostic sensitivity (100%), specificity (38%), positive predictive value (22%) and negative predictive value (100%) of the test[80].

Magnetic resonance imaging (MRI) and Magnetic resonance cholangiopancreatography (MRCP)

MRI with concurrent MRCP can provide three-dimensional reconstruction of the biliary tree by using magnetic resonance technology[105]. Multiple studies have demonstrated the utility of MRCP in evaluating patients with CC[106,107]. MRCP has diagnostic accuracy comparable to invasive cholangiographic techniques such as ERCP or percutaneous transhepatic cholangiography (PTC)[108-111]. A further advantage of MRCP over invasive cholangiographies is that it does not require biliary instrumentation[112]. Therefore, MRI along with MRCP is considered the radiological modality of choice for evaluating patients with suspected CC[113]. MRCP/MRI allows definition of the anatomy and extent of CC within the hepatobiliary system[108,110,114] vascular invasion, local lymphadenopathy and distant metastases[108,113,115]. Ideally, MRCP should be performed before decompressing the biliary tree[86]. ICC appear as a hypointense lesion on T1- and hyperintense on T2-weighted images with pooling of contrast within the tumor on delayed pictures as seen with CT[116,117]. On MRCP, ECC may appear as extrahepatic lesions with similar signal intensity of ICC on both T1- and T2-weighted images, in addition to proximal biliary dilatation[106,116]. A meta-analysis of 67 studies (4711 patients) evaluating MRCP performance in patients with suspected biliary diseases showed an overall sensitivity of 88% and specificity of 95%[107]. In a series of 99 patients with HCC, MRCP accurately determined the longitudinal extension of the tumor in 88% of patients[118]. In another smaller study, MRCP predicted the extent of biliary ductal involvement in 96% of cases with malignant hilar obstructions[115]. Regarding surrounding structures, MRI has been shown to have 66% accuracy for detection of lymph node metastases[119], 78% sensitivity and 91% specificity for portal vein invasion, 58%-73% sensitivity[120] and 93% specificity for arterial invasion[121]. In a comparative study the relationship of ICC to the vessels and surrounding organs was more easily evaluated on CT compared to MRI[89]. For patients affected by PSC and CC, the diagnostic capacity of MRI is enhanced by the presence of serum tumor marker Ca 19-9 above 20 U/mL; as a recent study has shown that the sensitivity of the test in this case was 96%, specificity 37%, positive predictive value 24%, and negative predictive value 98%[80].

Cholangiography

ERCP and PTC provide dynamic images but require invasive access to the biliary system. Both techniques can detect biliary abnormalities and determine the location and extent of ECC within the biliary tree. The choice between PTC and ERCP is generally dictated

by the availability of local expertise and the anatomical characteristics of the tumor[69]. In patients with complete biliary obstruction, ERCP often cannot assess the proximal biliary tree while PTC cannot assess the distal extent of the tumor[33,122].

The sensitivity and specificity of cholangiography range between 75%-85%, and 70%-75%, respectively[109,110] with accuracy of 95%[123]. Recent data have shown that in the presence of PSC, the association of an elevated level of serum Ca 19-9 increases the diagnostic utility of ERCP as its sensitivity was 91%, specificity 69%, positive predictive value 42%, and negative predictive value was 96%[80]. A drawback of these invasive procedures is the risk of complications such as post-ERCP pancreatitis (4%-10%)[123], bacteriobilia (30%-100%)[73], bleeding, sepsis, vascular injury and death[124]. On the other hand, ERCP and PTC have the advantage of providing brush cytology and bioptic specimens that can confirm the diagnosis of CC. The sensitivity of biopsy and brush cytology for diagnosing CC has been low due to the desmoplastic reaction associated with the tumor which is characterized by the presence of few malignant cholangiocytes within an extensive fibrous stroma[11]. In a large prospective study, the sensitivity of routine cytology varied from 9%-24% and the specificity varied from 61%-100% with a high rate of inter-pathologist variation; the best diagnostic yield was obtained when the pathologists were aware of the patient's clinical condition[125]. This was recently confirmed by a study from the Mayo Clinic which showed that in patients affected by PSC, the simultaneous presence of an elevated serum tumor marker level (Ca 19-9 above 20 U/mL) increased the sensitivity (50%), specificity (97%), positive predictive value (86%) and negative predictive value (88%) of cytological specimens[80]. In another study, repeated brushing appeared to be a valuable strategy to improve the sensitivity of cytological analysis up to 44%[126]. Endoscopic transpapillary forceps biopsies had a diagnostic sensitivity of 52% and a specificity of 100%[127]. Advanced cytologic techniques, including digitized image analysis (DIA) and fluorescence in situ hybridization (FISH), have been recently used to increase the sensitivity of cytology[128] especially in patients with PSC[80]. The DIA technique quantitates nuclear DNA via special stains to assess the presence of aneuploidy, whereas FISH analysis detects chromosomal polysomy by using fluorescent probes. In a prospective study, DIA increased the sensitivity from 18% to 39% but decreased the specificity from 98% to 77%[129]. In another comparative study, FISH increased the sensitivity from 15% to 34% compared to routine cytology, with similar specificities (91% for FISH and 98% for routine cytology)[130]. For patients with PSC, the presence of elevated serum level of Ca 19-9 (above 20 U/mL) increases the diagnostic capacity of DIA and FISH; as a recent study measuring these parameters has shown that their sensitivity was 57% and 86%, specificity 94% and 83%, positive predictive value 89% and 80%, and negative predictive value was 74% and 88%, respectively[80]. The use of peroral cholangioscopy

(POCS) or choledochoscopy has been shown to improve the diagnostic capacity of ERCP by directing tissue sampling. Fukuda et al[131] reported a sensitivity of 100% and a specificity of 87% for diagnosing the etiology of bile duct strictures by adding POCS to ERCP. At this moment, the availability of POCS is limited to a few centers due to lack of expertise and the high costs of instrumentation. The introduction of new technologies such as SpyGlass®, a single operator peroral cholangiopancreatoscopy, has eliminated the need for two ERCP operators and has the potential of becoming an important tool to improve the diagnostic capacities of endoscopic techniques, and it is currently under investigation[132-134].

Endoscopic ultrasound (EUS)

EUS is performed by using high frequency ultrasound probes placed on the endoscope. EUS has the advantage of interrogating tissues and organs in direct proximity to the stomach and duodenum, increasing the ability to detect abnormalities that would not be easily identified by percutaneous approach. In a prospective study of patients with suspected CC, EUS had a diagnostic sensitivity of 79% and specificity of 62%[111]. This was confirmed in a recent meta-analysis where EUS had sensitivity and specificity of 78% and 84%, respectively[135]. Two of the most attractive features of EUS are the ability to perform direct-guided fine needle aspirations (FNA) of the tumors in patients with negative cytology or the ability to sample enlarged lymph nodes for preoperative staging[136-138]. However, caution should be applied in patients with potentially curative CC as this approach has some risk of peritoneal seeding[65,130]. A recent prospective study evaluated the diagnostic yield of EUS-guided FNA of suspected HCC in potentially operable patients with negative brush cytology. The study showed sensitivity and specificity of 89% and 100%, respectively, and changed the preplanned surgical approach in 61% of patients[136]. In another prospective study, EUS-guided FNA of suspected CC reported a diagnostic sensitivity of 86%, with a specificity of 100%. In the same study, EUS-guided FNA had a positive impact on the treatment management of 84% of patients[139].

Intraductal ultrasound (IDUS)

IDUS is performed by using high frequency US probes placed into the common bile duct under ERCP guidance[140]. Malignant biliary strictures often appear on IDUS as a hypoechoic infiltration of the ductal wall with irregular margins[141,142]. In a prospective study of 62 patients with biliary strictures, IDUS had a diagnostic sensitivity of 90% and specificity of 93%[143]. In another study by Stavropoulos et al[144], IDUS increased the diagnostic accuracy of ERCP from 58% to 90% in a series of patients with biliary strictures and no mass detected on CT.

Positron emission tomography (PET)

PET is a non-invasive imaging modality that provides

functional images by detecting radiotracer 18F-fluo-rodeoxyglucose (FDG) uptake in neoplastic cells[145]. Currently it is considered a standard modality for the staging of many malignancies[146]. In the last decade, integrated PET and CT imaging systems (PET/CT) have combined the ability to obtain anatomical and functional images[146,147]. PET and PET/CT are proven to be useful in the diagnosis and staging of CC. In a recent study, PET showed sensitivity and specificity of 90% and 78% respectively[148]. In another study by Anderson *et al*[149], PET had sensitivity of 85% for CC measuring at least 1 cm in size although its sensitivity was only 18% for infiltrating CC. These values were confirmed by Kluge *et al*[150] who reported sensitivity of 92% and specificity of 93% for the detection of any type of CC by PET scan. A more recent study has shown that the sensitivity of PET/CT is correlated with the stage of CC as the sensitivity of the study was 25% for T2 tumors, 70% for T3 tumors and 66.7% for T4 tumors[151]. The rate of detecting distant metastases by PET and PET/CT in patients with CC is in the range of 70% to 100%, while the detection of regional lymph node metastases is only about 12%[152]. The sensitivity and specificity of PET/CT for detecting lymph node metastasis and distant metastasis were 41.7% and 80%, and 55.6% and 87.5%, respectively[146]. Another study from the Memorial Sloan Kettering Cancer Center has shown that PET/CT had an overall sensitivity for identifying the primary tumor of 80% (78% for CC and 86% for gallbladder cancer) and changed management in nearly a quarter of all patients[153]. PET has been shown to be useful in monitoring tumor response to treatment. In a small series by Chikamoto *et al*[154], PET had a sensitivity of 80% for detecting local recurrence after resection in patients with HCC. One of the limitations of PET is that patients with biliary inflammatory conditions such as PSC or cholangitis may have false positive results[152,155] while patients with mucinous CC may have falsely negative scans due to poor uptake of FDG[155].

Optical coherence tomography (OCT)

OCT is a new technique that produces cross-sectional images using infrared light. Preliminary studies have demonstrated the ability of OCT to generate high resolution images of the biliary tree that correlate with histological findings[156,157]. OCT has the potential to identify early CC[104] but it is not widely available except in a few centers. Therefore the role of OCT in the diagnostic workup of CC is not yet established.

Non diagnostic work-up

Non-diagnostic cytology or biopsy results should not rule out CC in the presence of appropriate clinical and radiological findings[73]. In the absence of other explainable causes of biliary strictures, patients should be considered to have CC and treated as such, accepting that 10% to 15% will have benign lesions on final pathology[158,159]. For high risk patients, no surveillance or screening programs have been validated. Some authors advocate annual follow up with non-invasive modalities (tumor markers and radiological tests), reserving invasive methods only when cytology and bioptic specimens or stenting are indicated[160].

TUMOR SPREAD

Understanding the patterns of spread of CC is essential for staging and treatment planning. CC can spread along biliary ducts, invade perineural and vascular tissues, spread directly into adjacent structures, invade lymph nodes or develop distant metastasis. Longitudinal extension of CC consists of mucosal (superficial) or submucosal (invasive) infiltration depending on the tumor growth pattern. Mucosal extension is predominantly seen with papillary (intraductal) and nodular (mass-forming) tumors, while submucosal extension is mainly seen with sclerosing (infiltrating) tumors[161]. The length of longitudinal extension is determined by the type of invasion, with a mean length of 6-10 mm for the submucosal spread and 10-20 mm for the mucosal spread[162]. Therefore, a gross surgical margin of more than 1 cm in the infiltrating type and more than 2 cm in the papillary and nodular types is recommended to achieve negative microscopic resection margins. One of the special characteristics of CC is the presence of perineural invasion that is seen in about 75% of cases[163,164]. Perineural invasion is a prognostic factor for poor survival[164,165]. In a retrospective review by He *et al*[164], the 5-year survival rate was 47% for patients without perineural invasion compared to 13% for those with perineural invasion. HCC can spread directly into the hepatic parenchyma and the hepatoduodenal ligament where the proper hepatic artery and the portal vein are in close proximity to the bile duct, while distal ECC may directly infiltrate into the pancreas or the duodenum[166]. Up to 80% of HCC have extension into the liver parenchyma[166,167] by direct infiltration or by longitudinal extension along the biliary ducts[168]. The latter mechanism explains the caudate lobe involvement by HCC and tumors involving the left hepatic duct[169]. Hence, the practice of partial hepatectomy with caudate lobectomy for the surgical treatment of patients with hilar tumors is associated with improved survival[168]. Tumors at the biliary confluence involve the portal vein in 30% of cases and often result in hepatic lobar atrophy[166,167]. The significance of portal vein involvement in patients' survival is controversial. Some studies have shown that tumor invasion of the portal vein has a negative impact[170,171] while other investigators reported opposite findings[166]. This is most likely due to the fact that patients with portal vein invasion may tolerate more extensive surgical resections as the contralateral lobe becomes hypertrophied, therefore decreasing the risk of perioperative mortality and enhancing the chances of negative resection margins. Lymph node metastases usually involve the regional hilar nodes and to a lesser extent the para-aortic lymphatic nodes[172]. The prevalence of lymph node involvement is approximately 45% for all CC with distal ECC having the highest incidence of nodal metastases[68,172]. Several studies have confirmed

Table 4 AJCC staging of ICC			
Stage	**Tumor**	**Node**	**Metastasis**
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IIIC	Any T	N1	M0
IV	Any T	Any N	M1

T1: Solitary tumor without vascular invasion; T2: Solitary tumor with vascular invasion or multiple tumors none > 5 cm; T3: Multiple tumors > 5 cm or tumor involving a major branch of the portal or hepatic vein(s); T4: Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum; N0: No regional lymph node metastasis; N1: Regional lymph node metastasis; M0: No distant metastasis; M1: Distant metastasis. AJCC: American Joint Committee on Cancer; ICC: Intrahepatic cholangiocarcinoma.

Table 5 AJCC staging of ECC			
Stage	**Tumor**	**Node**	**Metastasis**
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1-T3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

Tis: Carcinoma *in situ*; T1: Tumor confined to the bile duct histologically; T2: Tumor invades beyond the wall of the bile duct; T3: Tumor invades the liver, gallbladder, pancreas, and/or unilateral branches of the portal vein (right or left) or hepatic artery (right or left); T4: Tumor invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures, such as the colon, stomach, duodenum, or abdominal wall; N0: No regional lymph node metastasis; N1: Regional lymph node metastasis; M0: No distant metastasis; M1: Distant metastasis.

Table 6 Proposed T-Stage criteria for hilar cholangio-carcinomas (MSKCC)	
Stage	**Criteria**
T1	Tumor involving biliary confluence with or without unilateral extension to second-order biliary radicles
T2	Tumor involving biliary confluence with or without unilateral extension to second-order biliary radicles and ipsilateral portal vein involvement with or without ipsilateral hepatic lobar atrophy
T3	Tumor involving biliary confluence with bilateral extension to second-order biliary radicles; or unilateral extension to second-order biliary radicles with contralateral portal vein involvement; or unilateral extension to second-order biliary radicles with contralateral hepatic lobar atrophy; or main or bilateral portal vein involvement

that lymphatic tumor involvement is an important prognostic factor. Survival rates for patients undergoing surgical resection with positive lymphatic invasion at 5 years are 10% to 15% in comparison to 30% to 40% for patients without lymph node metastasis[164,172]. Presence of distant metastases (e.g. lung, bone, peritoneal, distant lymph nodes) is observed in 30% of patients at the time of diagnosis and is associated with survival of only a few months[166].

STAGING

ICC and ECC are staged differently.

ICC
ICC are classified as primary liver malignancies in the new American Joint Committee on Cancer (AJCC) staging system, also known as the TNM staging (Table 4)[173]. The AJCC staging system for primary liver tumors was based on data provided by patients affected by hepatocellular carcinomas and therefore is not sufficiently accurate for ICC[174]. A new staging system for ICC was proposed by Nathan *et al*[174] based on the number of tumors, vascular invasion, lymph node status and presence of metastatic disease. The presence of multiple tumors may be indicative of satellite neoplastic deposits or intrahepatic metastatic disease from hematogenous or lymphatic spread; similarly to vascular and lymph node invasion, it is associated with poor survival.

ECC
Giving the proximity of ECCs to the portal vein and hepatic artery, the goal of staging is to determine the local extent of the disease as it predicts resectability and the extent of the resection. The AJCC staging system for ECC (Table 5)[173] is based on pathological data useful in identifying the patients' prognosis but with little applicability for assessing the feasibility of surgical treatment[174]. Bismuth-Corlette classification for HCC is useful for describing the tumor location and its spread within the biliary tree but it is not predictive of resectability. The Memorial Sloan-Kettering Cancer Center (MSKCC) has proposed a staging system known as T-stage criteria[174]. The MSKCC staging system is based on the location and extent of ductal involvement, presence or absence of portal vein invasion, and presence or absence of hepatic lobar atrophy irrespective of metastases or lymph node status (Table 6). The MSKCC staging system for HCC correlates with resectability and survival, as 59% of T1 lesions are resectable with median survival of 20 mo compared to 0% resectability for T3 lesions with a median survival of only 8 mo[174].

THERAPY

Surgical resection
Tumor resection is the only potential cure for CC and the median survival of patients with unresectable disease is 6 to 12 mo[26]. All patients with resectable ICC and HCC, and the majority of patients with ECC, require partial hepatectomy to increase the chances of negative resection margins. Preoperative patients' evaluation includes an extensive assessment of their fitness for major surgery, the absence of any metastatic disease and the possibility of resection margins free from cancer[175]. If any of these conditions are not satisfied, surgical therapy is not indicated and palliative modalities should be recommended.

Table 7 Criteria for unresectability of HCC

Local tumor invasion
  Bilateral hepatic duct involvement up to secondary biliary radicles
  Encasement or occlusion of the main portal vein
  Unilateral tumor extension to secondary biliary radicles with
  contralateral portal vein or hepatic artery encasement or occlusion
  Hepatic lobar atrophy with contralateral portal vein or hepatic artery
  encasement or occlusion
  Hepatic lobar atrophy with contralateral tumor extension to
  secondary biliary radicles
Metastatic disease
  Lymph node metastases beyond the hepatoduodenal ligament (N2
  lymph nodes)[1]
  Distant metastasis (e.g. lung, liver, peritoneal)

[1]Peripancreatic, periduodenal, periportal, celiac, or superior mesenteric lymph nodes.

Table 8 Survival rates after resection of ICC			
Author (yr)	Resections (*n*)	Overall 5-year survival (%)	R0 5-year survival (%)
DeOliveira *et al*[67], 2007	34	40	63
Miwa *et al*[195], 2006	41	29	36
Jan *et al*[196], 2005	81	15	NR
Ohtsuka *et al*[197], 2003	50	23	NR
Uenishi *et al*[198], 2001	28	27	67
Inoue *et al*[199], 2000	52	36	55
Yamamoto *et al*[200], 1999	83	23	53
Madariaga *et al*[201], 1998	34	35	41

NR: Not reported.

Preoperative patient preparation

Many patients are not considered surgical candidates because of the presence of comorbidities or advanced age. A patient's performance status, nutritional conditions, and comorbidities need to be carefully evaluated before considering surgery[176]. A retrospective review of patients with resected HCC showed that the presence of preoperative serum albumin less than 3 g/dL was a significant predictive factor for high postoperative mortality[177]. In the same study, a preoperative serum total bilirubin above 10 mg/dL was associated with lower survival rates[177]. The role of preoperative biliary drainage (PBD) in jaundiced patients remains controversial. A recent meta-analysis failed to demonstrate any benefit[178]. Furthermore, PBD seems to increase the risk of perioperative infections and a longer postoperative hospital stay[124,178].

Nevertheless, prolonged preoperative biliary obstruction is associated with increased postoperative morbidity and mortality after hepatic resection due to the presence of severe cholestatic liver dysfunction[177,179]. Currently, preoperative PBD is not routinely recommended, but it has been shown to be beneficial in the presence of cholangitis, severe malnutrition, coagulation abnormalities[180,181] and when patients require major hepatic resection[175,182]. When preoperative drainage is performed, definitive surgery should be deferred for a few weeks to allow sufficient restoration of hepatic function[168]. The use of liver volumetric and/or hepatic functional studies is warranted when anticipating an extended hepatic resection, to estimate the future liver remnant and minimize the risk of liver failure caused by insufficient function or small residual liver parenchyma.

Assessment of resectability

Meticulous interpretation of all the available clinical and radiological data is recommended to determine resectability and avoid unnecessary interventions. Despite the improvement of diagnostic modalities, about 16%-25% of patients are found to have more extensive disease preventing resection at the time of laparotomy[68,183]. The major determinants of resectability

are the extent of tumor within the biliary tree, the amount of hepatic parenchyma involved, vascular invasion, hepatic lobar atrophy, and metastatic disease[166,179]. A review of 294 cases of CC demonstrated that resectability rates are higher for more distal tumors[69]. The determination of resectability is most challenging in patients with HCC. It is reported that about half of patients with HCC deemed to be resectable preoperatively have unresectable disease when explored[174]. The radiological criteria defining unresectability in patients with HCC are listed in Table 7[174,175]. With regard to distal ECC and ICC, AJCC stages III and IV are generally considered unresectable (Table 8).

Generally, invasion of the main portal vein or invasion of the vasculature supplying the planned hepatic remnant preclude resection. Nevertheless, recent reports have shown that en-bloc resection with vascular reconstruction may achieve negative margins and potential cure with only 10% perioperative mortality in very selected patients[184,185]. The application of staging laparoscopy has been recently advocated as it can reduce the number of unnecessary laparotomies by identifying metastatic lesions in the liver and in the peritoneal cavity[186]. The yield of laparoscopy for detecting unresectability in patients with potentially resectable CC on preoperative imaging modalities is about 25% with an overall accuracy of 50%[187,188]. Moreover, laparoscopy offers the addition of intraoperative hepatic US, which can increase the diagnostic yield up to 42%[189]. One of the limitations of laparoscopy is the inability to detect vascular or nodal involvement[188,189]. Peritoneal washings to obtain cytology specimens have not been shown to predict occult metastasis in patients with CC[190]. Ultimately, true resectability is determined after a complete abdominal exploration.

Operative procedures and survival

The goal of surgery is to obtain complete excision of the tumor with negative histological margins (R0 resection), as this is associated with marked survival advantages compared to margin positive resections (R1 or R2 resection)[26,68,176,191]. To confirm histologically-negative margins, many authors advocate the use of intraoperative frozen section examinations of the bile ducts[174]. A very important study from the MSKCC has recently evaluated the clinical significance of intraoperative frozen section for patients affected by HCC[192]. The primary aim of

Table 9 Survival rates after resection of HCC

Author (yr)	Resections (*n*)	Liver resection (%)	R0 resection (%)	Overall 5-year survival (%)	R0 5-year survival (%)
Hasegawa et al[213], 2007	49	92	78	40	50
DeOliveira et al[67], 2007	173	20	19	10	30
Dinant et al[214], 2006	99	38	31	27	33
Hemming et al[205], 2005	53	98	80	35	45
Rea et al[208], 2004	46	100	80	26	30
Kawasaki et al[182], 2003[1]	79	96	68	NR	40
Kawarada[215], 2002	87	75	64	26	NR
Jarnagin et al[166], 2001	80	78	78	37	NR
Tabata et al[216], 2000	75	71	60	23	40
Kosuge et al[217], 1999	65	88	52	35	52
Miyazaki et al[218], 1998	76	86	71	26	40

[1]Five-year survival for patients with R1 resection is 6%; NR: Not reported.

Table 10 Survival rates after resection of distal ECC

Author (yr)	Resections (*n*)	Overall 5-year survival (%)	R0 5-year survival (%)
DeOliveira et al[67], 2007	229	23	27
Cheng et al[219], 2007	112	25	26
Murakami et al[224], 2007	36	50	62
Yoshida et al[225], 2002	26	37	44
Fong et al[222], 1996	45	27	54[1]

[1]Patients had node negative tumors as well.

this study was to assess the importance of obtaining frozen sections of the bile duct margins for the planning of the extent of the surgical dissection. Frozen sections were obtained in 101 patients: among them 20 (19.8%) had positive and 81 (80.1%) had negative results. Among the patients who had negative frozen sections, 8 (9.8%) individuals were found to have positive margins at subsequent histopathology. In this study, intraoperative frozen section was shown to be 71.4% sensitive, 100% specific, and with a positive predictive value of 100% and negative predictive value of 80.2%[192].

ICC

Surgical therapy for ICC is based on the same principles used for hepatic resections performed for hepatocellular carcinomas or secondary tumors. The operative approach should be aimed at ensuring R0 resection margins whenever it is possible. Lymph node dissection during resection of ICC is not recommended as it does not improve patients' survival[193,194]. Current outcomes after surgical resection have improved in comparison to historical data with 5-year survival rates ranging from 20% to 40% (Table 9)[195-201]. Predictors of poor outcomes include: positive resection margins, lymphatic and vascular invasion and periductal infiltrating disease[202,203]. The most common site of recurrence after surgical resection is within the liver[196].

HCC

Curative surgery of HCC usually requires the excision of the extrahepatic bile duct, regional lymphadenectomy, cholecystectomy and in most cases some sort of partial hepatectomy including the caudate lobe, especially for tumors mainly extending in the left hepatic duct[174,207]. The rationale behind performing partial hepatectomies in HCC is to ensure histologically negative margins. Several studies have shown that this strategy increases R0 resections in up to 80% of patients[174,182,205]. Extended lymphadenectomy is not recommended as there is no evidence showing survival advantage[168,172].

Radical resection of HCC has 5%-10% perioperative mortality rate, especially when extended hepatectomy (5 or more segments) is required[174,206-208]. This partly relates to the increased rate of postoperative liver failure with major hepatic resections. Portal vein embolization (PVE) is a valuable preoperative measure when anticipating extensive liver resections with subsequent small hepatic residual volume[209]. A compensatory hypertrophy of the remnant hepatic parenchyma is induced by selectively occluding the main portal vein branch to the lobe that will be resected. This can increase the volume of the anticipated liver remnant by 12%-20%, thereby reducing the rate of postoperative liver dysfunction[210,211]. PVE is useful when the anticipated liver remnant volume is less than 20%-25% of the total liver volume in patients with normal liver function, and when the anticipated liver remnant volume is 40% or less in patients with compromised liver function[212].

The average 5-year survival rates post-resection for HCC are 25%-40% (Table 10)[68,174,182,209,213-218]. Factors associated with favorable outcome include; R0 resection, no lymph node metastasis, absence of perineural invasion, and well-differentiated histological grade[174,185].

ECC

The same principle of achieving a negative resection margin applies to ECC. The resectability rate has been reported as being up to 90% with distal extrahepatic tumors[68,219]. Complete removal of distal ECC usually requires a pancreaticoduodenectomy (Whipple procedure)[73,220,221]. Even in these circumstances, extended lymphadenectomy is not justified as it does not provide survival advantages and it is associated with increased perioperative morbidity[222]. Segmental bile duct excision is rarely an option, except for CC located in the middle of the common duct in the absence of periductal invasion or spread to the surrounding structures. Only 10% of patients undergoing bile duct excision alone obtain curative resection margins on final pathology[222,223]. Most commonly, when approaching patients with CC arising midway along the extrahepatic duct, surgeons should assess whether a pancreaticoduodenectomy or a partial hepatectomy is more appropriate with regard to the tumor extension. In these patients, curative resections are associated with a 25%-50% 5-year survival rate (Table 10)[68,220,223-225]. The main determinants of poor outcomes are positive surgical margins and lymph node involvement[220,223]. Other factors associated with unfavorable prognosis include pancreatic invasion, duodenal invasion, perineural invasion, and a poorly-differentiated histology[68,220].

Liver transplantation

Transplantation is an emerging therapy for unresectable CC without evidence of metastatic disease. Candidates are individuals who would require a total hepatectomy to achieve clear margins and those with underlying liver failure precluding hepatic resection. The early experience of transplantation for CC reported early recurrence rates of more than 50% and a 5-year survival of 10%-20%[226-228]. More recently, in highly selected patients undergoing neoadjuvant protocols, promising results have been reported. In 2002, Sudan *et al*[229] reported a series of 11 patients transplanted for CC after neoadjuvant chemoradiation with 45% tumor free survival and median follow up of 7.5 years. Similar reports have been reported by Becker *et al*[230] who observed a 45% 5-year survival for patients who were diagnosed as being affected by CC prior to undergoing transplantation, and a 33% 5-year survival was observed by Sotiropoulos *et al*[231] in Germany. At the Mayo Clinic, Rosen *et al*[232,233] have developed a liver transplantation protocol for HCC that provides a disease-free 5-year survival of 82%. This protocol is aimed at treating unresectable HCC or CC in PSC patients. To be eligible for this protocol, the diagnosis of CC is confirmed histologically, considered unresectable and with no evidence of metastatic disease. Eligible patients receive neoadjuvant chemoradiation therapy followed by staging laparotomy to rule out metastatic disease followed by living-related or cadaveric liver transplantation. Currently, the use of liver transplantation for the treatment of CC is reserved only for highly selected patients in specialized centers.

ADJUVANT THERAPY

The use of postoperative chemotherapy, radiotherapy or chemoradiation therapy have been evaluated as means of improving disease-free survival in patients with resected tumors since CC have high rates of local and distant recurrence.

Adjuvant chemotherapy

Postoperative chemotherapy has failed to show significant survival benefits[234,235]. A recent multicenter RCT evaluated the effect of postoperative chemotherapy with mitomycin C and 5-fluorouracil (5FU) versus surgery alone for individuals affected by cancers of the pancreas and biliary system[236]. Among 508 patients post-R0 resection, 139 individuals were affected by CC and for these individuals no survival benefit was seen after chemotherapy treatment[237].

Adjuvant radiotherapy

The use of postoperative external beam radiation with or without intraoperative radiotherapy and intraluminal radiotherapy (brachytherapy) has been explored in the adjuvant setting without significant benefits after R0 resections[125,237,238]. On the other hand, several studies showed that adjuvant radiotherapy may benefit patients with positive resection margins[239-241]. Todoroki *et al*[241] showed that the 5-year survival in patients with

R1 resections was 34% when adjuvant radiotherapy (intraoperative and external beam) was used compared to 14% with surgery alone.

Adjuvant chemoradiation therapy

The radiosensitizing effect of chemotherapeutic agents has been evaluated in the adjuvant setting with positive results only for distal ECC. In a retrospective cohort study of 94 individuals who underwent resection for CC, 34% received postoperative chemoradiation[242]. Longer survival was seen in patients who received adjuvant therapy (median survival 41 mo *vs* 24 mo)[243]. Other retrospective studies demonstrated similar results and showed that patients with distal ECC had a superior survival advantage in comparison to more proximal CC following adjuvant therapy[243,244]. Recently, Hughes *et al*[245] have confirmed a slight 5-year survival advantage with postoperative chemoradiation therapy in patients with distal ECC compared with surgical resection alone (35% *vs* 27%). In line with these findings, Figueras *et al*[246] did not demonstrate a significant survival benefit with adjuvant chemoradiation therapy for HCC. These results need to be confirmed further with larger prospective trials. For ICC, evidence to support the use of adjuvant chemoradiation therapy is very limited. In a recent retrospective study of 3839 patients, Shinohara *et al*[247] have shown that the overall survival rate was significantly different between groups receiving surgery alone and surgery plus adjuvant radiation therapy ($P = 0.014$) and between radiation therapy alone and no treatment ($P < 0.0001$). The combination of surgery and adjuvant radiation therapy conferred the greatest benefit on overall survival (HR: 0.40; 95% CI: 0.3-0.47), followed by surgery alone (HR: 0.49; 95% CI: 0.44-0.54) and radiation therapy alone (HR: 0.68; 95% CI: 0.59-0.77) compared with no treatment.

There is a lack of RCT evaluating the utility of adjuvant therapy following R0 resections of CC. Moreover, most of the current studies are small and retrospective in nature and incorporated CC with cancers of the gallbladder and pancreas. Therefore, no standard adjuvant modalities are universally embraced for the treatment of CC.

Neoadjuvant therapy

The role of preoperative chemoradiation therapy has been evaluated in a small series of patients with ECC[248]. Among nine patients who underwent neoadjuvant therapy, McMasters *et al*[248] observed pathological complete response in 3 individuals and negative resection margins were obtained in all subjects. More recently, neoadjuvant therapy has been used in the setting of liver transplantation for CC with promising results. Further trials are required to better assess its efficacy.

PALLIATION

Nearly half of the patients with CC are considered candidates only for palliative treatments due to the advanced stage of their disease at the time of diagnosis or the

presence of significant comorbidities that prevent surgical therapy[68,174]. Therefore, palliation plays an important role in the management of these individuals. The primary aim of palliative interventions is to improve quality of life by relieving symptoms and prolonging survival by preventing cholestatic liver failure. In the presence of incurable CC, tissue diagnosis should be obtained whenever possible to direct palliative therapy planning.

Biliary drainage

Biliary obstruction is the major cause of morbidity and mortality in patients with CC. The goals of biliary decompression are to relieve jaundice, pain, pruritus, and to prevent cholangitis and cholestatic liver failure[249]. Different modalities are currently available to drain the biliary system and these include: endoscopic, percutaneous and surgical bypass. The ideal palliative biliary decompression should be effective, provide durable results, and have low risks of morbidity and mortality.

Biliary endoprosthesis (stenting)

Biliary stenting can be achieved endoscopically or percutaneously. Endoscopic biliary stenting is the most widely used method and the percutaneous approach is usually performed when endoscopic drainage fails or cannot be performed. Percutaneous stents can be either internal, external or both. External stents have the disadvantage of draining bile without the ability of enteric recycling and are associated with more discomfort and reduced quality of life. Little is known as to whether percutaneous or endoscopic biliary drainage have different overall efficacy in palliating patients with unresectable disease. Generally, only patients with advanced tumors that are totally obstructed are candidates for percutaneous external biliary drainage. A recent multicenter retrospective study from South Korea has shown that the placement of percutaneous self-expanding metallic stents across HCCs is associated with a higher success rate and lower risk of procedure-induced cholangitis[250].

Endoscopic stents can be either self-expanding metallic or plastic (polyethylene). Metal stents are more expensive than plastic stents but have larger diameters and provide better patency rates[251]. Metal stents can be either uncovered or covered by sealing the metallic mesh with a membrane which prevents tumor growth through the stent, increasing patency rates. Plastic stents often need to be changed at 2 to 3-mo intervals, while metal stents can remain patent up to 9 mo[252]. Several RCT have compared metal to plastic stents for the treatment of patients with inoperable malignant biliary obstruction[253,254]. These studies concluded that metal stents are more cost-effective for patients who are expected to survive more than 5 mo as they need less interventions and shorter hospitalizations[254,255]. Patency rates are generally higher for ECC[255] and metal stents provide superior palliation for HCC as compared to plastic stents[256,257]. Draining about 25% of the hepatic parenchyma is usually sufficient for adequate palliation in the absence of infection[250]. A RCT comparing unilateral versus bilateral drainage in patients with malignant hilar obstruction found that drainage of one functional hepatic lobe is sufficient to relieve obstruction with no difference in complication and survival rates[258]. It is important to note that stents placed for hilar lesions will require re-intervention in about 30% of patients due to stent occlusion[259,260]. A RCT comparing covered to uncovered stents in patients with unresectable distal biliary malignancies showed that the patency of covered stents was significantly higher than that of uncovered stents[261]. However, multiple studies report an increased risk of cholecystitis (5%) with the covered stents due to cystic duct occlusion[262].

Surgical biliary drainage

Biliary-enteric anastomosis can be performed by open or laparoscopic approach. Studies comparing surgical to non-surgical biliary drainage showed similar overall palliative effects but with higher perioperative morbidity and mortality[263,264]. Surgical drainage has the advantage of superior patency rates and prevents the need for stent exchanges required when using endoscopic or percutaneous stents due to clogging[265]. Currently, the main candidates for surgical drainage are patients found to have unresectable CC at the time of exploration, individuals who are not able to undergo repeat endoscopic or percutaneous stent exchanges, and those who have long expected survival and who are fit for surgery[183,266].

Palliative radiotherapy

Palliative radiotherapy may benefit patients with locally advanced unresectable CC or those who have undergone palliative bypass in the absence of distant metastases. The use of palliative radiotherapy has beneficial effects on pain relief, biliary patency and overall patient survival[267,268]. The two most commonly used radiotherapy modalities are external beam radiation with 30 to 50 Gy, intraluminal brachytherapy with 10 to 20 Gy or the combination of both. Intraluminal brachytherapy is delivered by using iridium-192 seeds mounted on a catheter that is deployed across the tumor by endoscopic or percutaneous approach[269]. It appears that brachytherapy is able to deliver more effective doses of radiation without damaging the surrounding organs. Generally, the majority of studies that demonstrated benefit of radiotherapy used combinations of both modalities with median patient survival ranging between 9 and 14 mo[270-273]. Palliative radiotherapy is associated with increased incidence of complications such as cholangitis, gastroduodenitis and longer hospital stay in comparison to best supportive care and therefore it is not routinely used in many centers[274]. Moreover, higher doses of radiation (more than 55 Gy) may be required to obtain an improved survival, with increased toxicity rates[275]. Controlled studies are required to better evaluate the effectiveness and safety of these palliative treatments. For ICC, brachytherapy can be delivered by radioembolization with yttrium-90 microspheres[276]. This approach has been shown to provide partial response in 27% of patients and stable disease in 68% with limited side effects; therefore it is not surprising that it has become the leading modality for palliation of CC in centers where this technique is available[277].

Palliative chemotherapy

There is no standard chemotherapy option for patients with CC. Patients with widespread disease considered for palliative chemotherapy undergo treatment in an attempt to control the disease and improve their overall survival. Owing to the lack of RCT and the retrospective nature of observational studies with heterogenous patient populations currently available, the interpretation of the survival benefit of palliative chemotherapy is difficult. Various chemotherapeutic agents with different dosing regimens have been tested with overall poor survival improvement. Historically, 5FU was the first chemotherapeutic agent used for palliation of CC patients with only 10% response rates when used alone. Several subsequent studies have evaluated 5FU in combination with other agents such as leucovorin, interferon-alpha, cisplatin, and oxaliplatin, with an overall response rate of 25% to 55% and a median survival ranging between 6 and 12 mo[278-281]. Multiple phase II trials have evaluated the use of oral 5FU prodrugs (uracil-tegafur and capecitabine) in patients with advanced CC[282,283]. For example, the combination of capecitabine and cisplatin had mild toxicity and produced a response in 41% of patients with a median survival of 12 mo[283]. Gemcitabine proved to have good efficacy as a single agent in biliary malignancies with response rates of 30%[284]. Several gemcitabine-based combinations, including cisplatin, capecitabine, and oxaliplatin have reported response rates up to 36% and median survival of 10 to 15 mo[285-287]. Finally, a recent analysis of all the published chemotherapy trials in individuals affected by advanced CC from 1985 to 2006 concluded that gemcitabine combined with platinum compounds (cisplatin or oxaliplatin) had the best patient response rates[288,289]. Recently, the roles of transcatheter arterial chemoembolization (TACE) and transcatheter arterial chemoinfusion (TACI) have been assessed for patients affected by unresectable ICC[290,291]. Although TACE and TACI with gemcitabine, cisplatin and doxorubicin in different combinations[292] are well tolerated, survival benefits have not been proven in large studies and will require further evidence before becoming widely accepted in the scientific community.

Photodynamic therapy (PDT)

PDT is an emerging palliative strategy based on the intravenous administration of photosensitizing agents that preferentially accumulate in malignant cells. After the delivery of these photosensitizing agents, specific wavelengths of light are administered causing activation of the photosensitizer and thus tumor cell necrosis[293]. The depth of tumor necrosis obtained by this technique is between 4 mm and 6 mm[294]. This modality is currently used as a palliative measure in conjunction with biliary stenting for nonresectable CCs. Improvements in quality of life, biliary drainage, and survival in patients with advanced CCs post-PDT have been reported in several case series[294]. Furthermore, a RCT compared PDT with endoscopic stenting to stenting alone in patients with unresectable CC[295]. The study was terminated prematurely because PDT proved to be markedly superior to simple stenting. The PDT group in that trial had higher median survival (493 d *vs* 98 d), improved biliary drainage and better quality of life than the stenting alone group[296]. Recently, PDT was investigated as a neoadjuvant modality before surgical resection of advanced HCC in 7 patients[296]. Tumor-free resection margins were achieved in all patients with a 1-year recurrence-free survival rate of 83%[297]. A recent study confirmed that the use of PDT as a neoadjuvant therapy is safe and can downstage tumors from unresectable to resectable[297]. The main side effects of PDT include photosensitivity caused by the administration of photosensitizer agents and cholangitis related to biliary instrumentation[294,298].

Other palliative measures: Several other palliative modalities have shown some benefits in selected groups of patients. Radiofrequency ablation has been used for patients unfit for surgery who have small intrahepatic CC[299]. In a single-centre cohort of patients with unresectable intrahepatic CC, TACE has shown some survival advantage in comparison to best supportive care (median survival: 23 mo)[300]. Hepatic arterial chemoinfusion offers tumor-directed chemotherapy and it has been proven to be safe[301] as has localized ablation of tumor cells by high intensity intraductal ultrasound[302]. Another promising area is the use of molecular targeting agents for chemoprevention and adjuvant therapy of CC such as cyclooxygenase-2 and nitric oxide inhibitors[303]. The clinical utility of these emerging therapies needs further investigation before gaining wide acceptance.

CONCLUSION

Over the last decades several advances have occurred in the fields of epidemiology, diagnostic modalities, medical and surgical treatment of CC as well as in palliation. The diagnosis, staging and further management of patients affected by this disease may be a complex issue and requires expertise in many fields. To optimize the outcome of patients with suspected or proven CC, a multidisciplinary approach is recommended.

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