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Advances in diagnosis and treatment of hilar cholangiocarcinoma – a review

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Hilar cholangiocarcinoma (HC) is a rare tumor that causes devastating disease. In the late stages, this carcinoma primarily invades the portal vein and metastasizes to the hepatic lobes; it is associated with a poor prognosis. HC is diagnosed by its clinical manifestation and results of imaging techniques such as ultrasound, computed tomography, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiography, and percutaneous transhepatic cholangiography. Preoperative hepatic bile drainage can improve symptoms associated with insufficient liver and kidney function, coagulopathy, and jaundice. Surgical margin-negative (R0) resection, including major liver resection, is the most effective and potentially curative treatment for HC. If the tumor is not resected, then liver transplantation with adjuvant management can improve survival. We conducted a systematic review of developments in imaging studies and major surgical hepatectomy for HC with positive outcomes regarding quality of life.

Key words: hilar cholangiocarcinoma • diagnosis • treatment • liver resection

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Background

Hilar cholangiocarcinoma (HC), also known as Klatskin tumor, occurs at the confluence of the right and left hepatic ducts. It is a rare, devastating, and highly malignant disease of the bile duct. The biliary tree is at high risk of HC development at the biliary confluence of the right and left hepatic ducts. HC is classified into 2 categories: extrahepatic cholangiocarcinoma, which only invades the hepatic hilum; and intrahepatic cholangiocarcinoma, which involves the intrahepatic duct, lobar duct, interlobular ductules, and canaliculi. On cholangiography, both extrahepatic and intrahepatic cholangiocarcinoma have similar features, and management for both involves resection of the tumor involving the biliary ducts [1]. Complete margin-negative (R0) resection is more curative in the early stage of HC than in the late stage. In the late stage, the tumor may be close to or invading the major vascular structures surrounding the bile duct, such as the portal vein, hepatic artery, and liver parenchyma. Most commonly, HC invades the portal vein, making surgical resection a high-risk procedure. Preoperative imaging is very important to establish a diagnosis, identify the level of obstruction, and stage the carcinomas; such imaging techniques include Doppler ultrasound, computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiography (ERCP), and percutaneous transhepatic cholangiography (PTC) [2]. Surgical management is the most effective and curative procedure for R0 resection and provides a better chance for long-term survival compared with conservative therapy [3,4]. Several advances in the diagnosis, therapy, and palliation of patients affected by HC have occurred during the last few decades, but HC remains the most difficult challenge for hepatobiliary surgeons. This review article focuses on the current imaging studies and surgical management of HC.

Imaging Studies

Clinically, most affected patients present with the symptom of jaundice. Imaging studies are beneficial to determine the level of biliary tree obstruction, identify the portion of the hepatic parenchyma with major vascular involvement, and evaluate metastasis to other organs. Abdominal ultrasound findings are often used as the first-line diagnostic criteria in clinical trials to confirm biliary duct dilatation, exclude stones, and identify the level of the obstruction. Dilatation of the intrahepatic bile ducts is the most frequently seen abnormality in patients with HC. In advanced cases, ultrasonography plays an important role in confirming tumor extension within the biliary tree and verifying major vascular involvement [5,6]. However, when the tumor involves the intrahepatic or perihilar duct, it cannot be fully diagnosed by ultrasound; thus, the extent of the tumor within the biliary tree could be missed. Color Doppler ultrasonography can be used to detect tumor-induced strictures of the bile duct, as well as compression and thrombosis in the hepatic artery and portal vein. Color Doppler ultrasound is beneficial in assessing portal venous invasion and hepatic parenchymal involvement.

Due to frequent interference by bowel gas, ultrasound examination of the bile duct may not always be successful. Endoscopic ultrasound (EUS) is performed 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 a percutaneous approach. In a prospective study of patients with suspected cholangiocarcinoma, EUS had a diagnostic sensitivity of 79% and specificity of 62% [7].

Intraductal ultrasound (IDUS) is performed using high-frequency US probes placed into the common bile duct under ERCP guidance [8]. Malignant biliary strictures often appear on IDUS as hypoechoic infiltrations of the ductal wall, with irregular margins [9,10]. In a prospective study of 62 patients with biliary strictures, IDUS had a diagnostic sensitivity of 90% and specificity of 93% [11].

In the current era of advanced imaging technology, it has become easier to obtain the same information as that obtained by previous invasive procedures. In most cases of hilar obstruction, abdominal CT is the standard evaluation technique with which to observe tumor size, tumor regularity, and liver atrophy and to perform liver volumetric analysis. Preoperative CT can provide the total hepatic volume for hepatic resection. High resolution is obtained when using thin-cut CT scans to observe local invasion, lobar atrophy, portal vein compression, regional and distal lymph node metastasis, and non-lymphatic distant metastasis. Serial transverse scans are sensitive for detecting intrahepatic tumors of >1 cm at the site of biliary obstruction, as well as lymphadenopathy [12]. CT is also helpful in the staging, preoperative planning, and evaluation of vascular encasement. However, in some cases of HC, visualization of the neoplasms is not definitive because they are too small to be detected, and evaluation of intraductal spread and detection of lymph nodes, and peripheral metastasis by CT is a suboptimal radiological investigation technique. CT cholangiography (CTC) was recently shown to be a promising modality for delineation of the biliary tree. In a large study, CTC was superior to conventional CT or US, and equal to ERCP for the diagnosis of HC [13]. One of the limitations of CTC is that optimal imaging quality depends on the secretory function of the liver [14].

MRCP is one of the best advanced technologies and has several advantages over CT. MRCP is a noninvasive imaging technique for biliary duct carcinoma. In recent clinical trials, MRCP was a powerful investigation method for the diagnosis of HC. It also provides important information on both obstructed and unobstructed bile ducts, as well as tumor extension within the

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Table 1. Bismuth-Corlette Classification System [26].

Bismuth-Corlette Classification for hilar cholangiocarcinoma	
Type I	Below the confluence
Type II	Confined to the confluence
Type IIIa	Extension into the right hepatic duct
Type IIIb	Extension into the left hepatic duct
Type IV	Extension into the right and left hepatic duct and multifocal bile duct tumor

biliary tree and periductal tissue. The combination of MRCP and magnetic resonance angiography can provide useful information about the involvement of hilar vascular structures [15,16]. Compared with ERCP, MRCP is a highly advanced and more frequently used technique for identification of the tumor site and position when assessing the resectability of HC [17,18].Importantly, it allows for observation of HC extension to the biliary tree and vessels, involvement of adjacent liver parenchyma, local lymphadenopathy, and distant metastasis [17]. MRCP is a non-invasive imaging technique for cholangiography and allows visualization of both the obstructed and unobstructed ducts, but both ERCP and PTC are invasive imaging techniques [19,20]. PTC is more desirable than ERCP because it more clearly delineates tumor involvement in the proximal biliary tree; it is often used for biliary decompression before surgical resection and can relieve jaundice for palliative therapy. ERCP is sometimes used as palliative therapy for placement of a stent in the presence of unresectable HC. In addition, ERCP and PTC have the advantage of providing brush cytology and biopsy specimens that can confirm the diagnosis of HC. ERCP and PTC are often used to evaluate and justify the possibility of major liver resection. The choice between PTC and ERCP is generally dictated by the availability of local expertise and the anatomical characteristics of the tumor [21].

Positron emission tomography (PET) is a non-invasive imaging modality that provides functional images by detecting uptake of the radiotracer 18F-fluorodeoxyglucose (FDG) in neoplastic cells [22]. PET is currently considered to be a standard modality for the staging of many malignancies [23]. In the last decade, integrated PET and CT imaging systems (PET/CT) have allowed for the acquisition of both anatomical and functional images [23,24]. PET and PET/CT have been proven useful in the diagnosis and staging of cholangiocarcinoma. In a recent study, PET showed a 90% sensitivity and 78% specificity [25].

Tumor Staging and Assessment for Resectability

Three basic systems are often used for the classification of peripheral HC worldwide: (1) the Bismuth-Corlette classification system [26], (2) the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) with tumor-node-metastasis (TNM) classification [27], and (3) the Memorial Sloan-Kettering Cancer Center (MSKCC) classification [28].

The Bismuth-Corlette classification system is commonly used in cases of biliary tree involvement [26] and to stage peripheral HC. However, in some cases it fails to provide complete information about vascular involvement, lymph node involvement, distant metastasis, and liver atrophy. This staging system is primarily used as a convenient guideline for the surgical approach (i.e., types I and II indicate local resection, type III indicates major liver resection, and type IV is a contraindication for resection), as shown in Table 1.

The TNM classification for extrahepatic bile duct tumors provides complete information on pathological findings; thus, it is also considered to be a pathological staging system, as shown in Table 2.

A preoperative clinical tumor staging system was finally introduced by Jarnagin and Blumgart [28,29]. This classification system is significant for the assessment of the radial and longitudinal extension of HC. The MSKCC classification system further classifies peripheral HC according to the 3 major factors of preoperative imaging studies: (1) the location and extent of biliary ductal involvement, (2) the presence or absence of portal vein involvement, and (3) the presence or absence of hepatic lobar atrophy, as shown in Table 3.

The most commonly used system is the Bismuth-Corlette classification of bile duct involvement, but it does not include crucial information such as vascular encasement and distant metastases. Other systems are rarely used because they do not provide several key pieces of information to guide therapy.

A new system was recently designed that reports the tumor size, extent of disease in the biliary system, hepatic artery and portal vein involvement, lymph node involvement, distant metastases, and putative remnant liver volume after resection [30]. This system aims to standardize the reporting of perihilar HC so that relevant information regarding resectability, indications for liver transplantation, and prognosis can be provided.

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Table 2. TNM Classification of extrahepatic bile duct tumors according to the AJCC/UICC 7th edition.

Primary tumor (T)			
TX	The primary tumor cannot be assessed		
T0	No evidence of a primary tumor		
Tis	Carcinoma *in situ*		
T1	The tumor is confined to the bile duct histologically		
T2a	The tumor invades the surrounding adipose tissue beyond the wall of the bile duct		
T2b	The tumor invades the adjacent hepatic parenchyma		
T3	The tumor invades unilateral branches of the portal vein or hepatic artery		
T4	The tumor invades the main portal vein or its branches bilaterally, the common hepatic artery, the second-order biliary radicals bilaterally, or the unilateral second-order biliary radicals with contralateral portal vein or hepatic vein involvement		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis (cystic duct, common bile duct, hepatic artery, and portal vein)		
N2	Metastasis to periaortic, pericaval, superior mesentery artery, and/or celiac artery nodes		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a–T2b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1–T3	N1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

Table 3. Tumor staging according to the MSKCC Classification [28].

Tumor stage (T)	Description
T1	The tumor involves the biliary confluence with unilateral involvement up to secondary biliary radicles. There is no portal vein involvement or liver atrophy
T2	The tumor involves the biliary confluence with unilateral involvement up to secondary biliary radicles. There is ipsilateral portal vein involvement or ipsilateral hepatic lobar atrophy
T3	The tumor involves the biliary confluence with bilateral involvement up to secondary biliary radicles, unilateral extension to secondary biliary radicles with contralateral portal vein involvement, unilateral involvement up to secondary radicles with contralateral hepatic lobar atrophy, or main / bilateral portal vein involvement

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Preoperative Biliary Drainage

Preoperative biliary drainage is extremely important in patients with hepatic insufficiency. If the biliary duct obstruction is not relieved, hepatic and renal dysfunction and coagulopathy may result [31–33]. In Asia, biliary drainage is the first step in the management of patients with HC before major liver resection [34–37]. However, in Western countries, the performance of biliary drainage is highly selective; endoscopic or percutaneous drainage of the catheters used for routine drainage may increase the risk of infectious complications and tumor seeding [34,38]. Preoperative biliary drainage is only indicated in patients with cholangitis, longstanding jaundice, or poor nutrition and in those in whom the insufficient liver volume is <40% of the total liver volume [39].

Surgical Treatment

Surgical management is the best option for cure of HC [29,37,40]. These carcinomas can be resected by the hepatobiliary surgical team; explorative laparotomy is needed for R0 resection with the hilar lymph nodes. If the tumor has extended to the peritoneum or involves para-aortic lymph node infiltration or bilateral hepatic lobe metastasis including the hepatic artery, portal vein, and inferior vena cava, then surgical resection is contraindicated; it is a high-risk procedure that cannot improve the patient's quality of life. Suspicious lymph nodes around the hepatic pedicles need to be dissected and analyzed by histopathology. After peritoneal spread is confirmed by frozen section histopathology, explorative laparotomy is performed. Staging laparoscopy is recommended to detect occult metastatic disease [41]. When the tumor involves the ipsilateral hepatic bile duct and vessels, en bloc resection of the cholangiocarcinoma and partial hepatectomy with negative histological margins can improve the survival rate of the patient [29,42].

Over the past 20 years, there has been an increase in the performance of hepatic resection in patients with HC. Major hepatic resection addresses both direct hepatic invasion and intraductal extension of HC to achieve negative radial and longitudinal resection margins. According to the Bismuth-Corlette classification, right hemihepatectomy is suggested for type I, II, and IIIa tumors that involve the common hepatic duct and right hepatic biliary tree [43]; left hemihepatectomy is recommended for type IIIb tumors that extend to the left confluence of the biliary tree; and central bisectionectomy or right and left trisectionectomy is indicated for type IV tumors that invade the right and left hepatic biliary trees [44]. However, it is uncertain whether major hepatic resection can improve survival for patients with Bismuth-Corlette type I or II hilar cholangiocarcinoma; others have reported no significant difference in survival between hepatectomy and bile duct resection alone for type I and II tumors [45]. This requires further evaluation in larger studies with longer follow-up prior to assessing the true impact of hepatectomy for these tumors.

When the carcinoma extends to the lower bile duct, the procedure is combined with pancreatoduodenectomy [1,37]. However, major hepatic resection is associated with a high risk of postoperative complications, including hepatic insufficiency and other problems. In the current era, the incidence of post-hepatectomy complications associated with liver failure has markedly decreased [4,34,35]. When emboli develop in the portal vein, additional aggressive vascular resection is indicated [35]. When the tumor invades the portal vein and hepatic artery, both vessel resection and reconstruction are indicated, which are now routinely performed when necessary.

The surgical technique is very important for resection of the connective tissue of the hepatoduodenal ligament with dissection of the lymph node [46,47]. Metastasis to regional lymph nodes is common and is an important prognostic factor influencing survival after resection for hilar cholangiocarcinoma. The 5-year survival rate was 30% for node-negative patients, 15% for patients with regional nodal metastases, and 12% for those with para-aortic nodal metastases [48]. Lymph node dissection includes the nodes within the hepatoduodenal ligament, those behind the pancreatic head, and those along the common hepatic artery. Extended lymph node dissection beyond the hepatoduodenal ligament is not recommended [49]. Patients with grossly involved lymph nodes beyond the hepatoduodenal ligament are considered to have unresectable disease.

The biliary duct drains from the caudate lobe and enters the right and left hepatic ducts. In most cases, the carcinoma extends to the caudate lobe, and isolated radical caudate lobectomy is thus routinely planned for curative treatment of HC. Retrospective studies have shown a decrease in local recurrence and improvement in 5-year survival when concomitant caudate lobe resection is performed [33,50]. Finally, the continuity of biliary drainage is restored with a Roux-en-Y hepaticojejunostomy.

Previous studies have shown that major hepatic resection can result in a mortality rate of 0% to 15% and morbidity rate of 14% to 76%, as shown in Table 4 [28,34,51–65].

Palliative Therapy

For patients in whom R0 resection cannot be performed, palliative therapy is the best choice to relieve jaundice and pruritus. Palliative therapy may involve endoscopic stenting,

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Table 4. Selected summary of patients who underwent curative resection and major liver resection.

Authors' names	Published year	Resections	Resectability (%)	Negative margin (%)	Liver resection (%)	Morbidity (%)	Mortality (%)	5 years survival rate (%)
Nimura et al.	1990	55	83	84	98	41	6	41
Nakeeb et al.	1996	109	56	26	14	47	4	11
Miyazaki et al.	1998	76	Not available	71	86	33	13	26
Neuhaus et al.	1999	80	Not available	61	85	55	8	22
Kosuge et al.	1999	65	72	52	80	37	9	33
Nimura	2000	142	80	61	90	49	9	26
Jarnagin et al.	2001	80	50	78	78	64	10	26
Kawarada et al.	2002	65	89	64	75	28	2.3	26
Capussotti et al.	2002	36	Not available	89	89	47.2	2.8	27.2
Kawasaki et al.	2003	79	75	68	87	14	1.3	22
Ijitsma et al.	2004	42	Not available	65	100	76	12	19
Hemming et al.	2005	53	50	80	98	40	9	35
Dinant et al.	2006	99	Not available	31	38	66	15	27
Baton et al.	2007	59	72	46	100	42	5	20
Konstadoulakis et al.	2008	59	81	68.6	86.4	25.5	6.8	34.9
Ito et al.	2008	38	55	63	53	32	0	33
Igami et al.	2010	298	70	74	98	43	2	42
Nagino et al.	2012	574	76.1	76.5	96.7	57.3	4.7	32.5

percutaneous stenting, or surgical bypass. Sometimes a combined approach is needed. Palliative therapy can also improve the survival rate with low morbidity [66,67]. Recent studies have reported a success rate of 69% to 97% with percutaneous or endoscopic biliary decompression [68,69]. If the tumor extensively invades the proximal biliary tree, endoscopic placement of a single stent is difficult and may not fully decompress the left and right hepatic ducts. Thus, multiple biliary stents must first be placed in the proximal duct, then in the distal duct [70,71].

Metal stents are preferred for patients with unresectable disease. Metal stents are more expensive than plastic stents, but have larger diameters and provide better patency rates [72–74]. Endoscopic stents can be either self-expanding metallic or plastic (polyethylene). 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 every 2 to 3 months, but metal stents can remain patent for up to 9 months [72].

In patients with HC, ERCP is associated with a greater risk of inadequate drainage of the biliary duct. It is also associated with a high risk of cholangitis and increased mortality. ERCP is technically very difficult for bilateral stenting procedures. Some patients with advanced tumors that are totally obstructing the bile duct are candidates for percutaneous external biliary drainage [68,75]. For these patients, external drainage is the best option for palliation, but is associated with various complications such as cholangitis if used for long-term treatment. PTC with percutaneous biliary drainage is the most ideal procedure for HC [76]. Drainage in both the right and left hepatic biliary system is maintained without failure in contrast medium. Advancement of a guide wire is sometimes performed for excessive drainage into the duodenum.

For HC, adjuvant chemotherapy and radiation therapy are discouraging and cannot improve the survival rate. Retrospective studies have suggested that transhepatic intraluminal brachytherapy and external beam radiotherapy may also give unimpressive results [75,77,78]. For HC, chemotherapy may be less effective than radiotherapy and shows a response rate of 10%

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to 21% [79,80]. The agents used include alpha interferon, leucovorin, 5-fluorouracil, and carboplatin.

Photodynamic therapy (PDT) is also used to treat HC. PDT involves the intravenous injection of porphyrin-based photosensitizers. These porphyrins form chelates with iron, magnesium, copper, nickel, and zinc. A laser light of a specific wavelength is then applied to the tumor bed and may cause tumor cell death. Uncontrolled studies have shown that PDT used for unresected bile duct cancer may improve the survival rate of patients with biliary decompression [81,82].

Liver Transplantation

The ideal therapy for HC is curative R0 resection [83]. When the tumor metastasizes or spreads, palliative therapy is indicated, but it is associated with a low survival rate [84]. When the tumor has extended to the common hepatic artery, portal vein, inferior vena cava, and contralateral hepatic lobes, it is unresectable. For example, Bismuth type IV tumors involve all of the hepatic duct and are unresectable; in this condition, liver transplantation is the best way to improve survival. Previous studies have shown that when the lymph nodule is not spreading and the tumor is locally restricted, liver transplantation has the best result [85,86]. No available selection criteria for patients with HC advise liver transplantation. In some cases, however, it can be recommended as the most appropriate treatment for HC. The Mayo Clinic protocol was recently developed with the intent to treat a highly selective group of patients with HC with a strict regimen of preoperative staging and neoadjuvant treatment followed by orthotopic liver transplantation [87]. Outcomes of 65 patients treated with this protocol showed 1- and 5-year survival rates of 91% and 76%, respectively.

Conclusions

Surgical resection is the best management for HC. Negative tumor margins with major hepatic resection can improve the survival rate of the patient. HC can be properly diagnosed by imaging studies such as CT, MRCP, ERCP, and PTC. We conclude that major hepatectomy for HC can increase the proportion of R0 resections and improve recurrence-free survival outcomes.

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