World Journal of Gastrointestinal Pathophysiology

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4291/wjgp.v5.i3.344

World J Gastrointest Pathophysiol 2014 August 15; 5(3): 344-354
ISSN 2150-5330 (online)

REVIEW

Perihilar cholangiocarcinoma: Current therapy

Wei Zhang, Lu-Nan Yan

Wei Zhang, Lu-Nan Yan, Department of Liver Surgery, Liver Transplantation Division, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China
Author contributions: Zhang W and Yan LN contributed equally to this work; Zhang W and Yan LN designed and performed the research; ZW wrote the paper.
Correspondence to: Lu-Nan Yan, MD, PhD, Department of Liver Surgery, Liver Transplantation Division, West China Hospital, Sichuan University, Wuhou District, Chengdu 610041, Sichuan Province, China. yanlunan688@163.com
Telephone: +86-28-81812453 Fax: +86-28-85423724
Received: January 16, 20104 Revised: April 11, 2014
Accepted: June 10, 2014
Published online: August 15, 2014

Abstract

Perihilar cholangiocarcinoma, which is a rare primary malignancy, originates from the epithelial cells of the bile duct. Usually invading the periductal tissues and the lymph nodes, perihilar cholangiocarcinoma is commonly diagnosed in the advanced stage of the disease and has a dismal prognosis. Currently, complete hepatectomy is the primary therapy for curing this disease. Perioperative assessment and available surgical procedures can be considered for achieving a negative margin resection, which is associated with long-term survival and better quality of life. For patients with unresectable cholangiocarcinoma, several palliative treatments have been demonstrated to produce a better outcome; and liver transplantation for selected patients with perihilar cholangiocarcinoma is promising and desirable. However, the role of palliative treatments and liver transplantation was controversial and requires more evidence and substantial validity from multiple institutions. In this article, we summarize the data from multiple institutions and discuss the resectability, mortality, morbidity and outcome with different approaches.

Key words: Cholangiocarcinoma; Klatskin tumor; Surgery; Liver transplantation; Therapy

Core tip: Perihilar cholangiocarcinoma is a type of malignant tumor with vague and insidious symptoms, and is often diagnosed at an advanced stage. Currently, negative margin resection (R0) is the only way to cure patients with perihilar cholangiocarcinoma. In this article, we describe the surgical procedure and the criteria for operation and illustrate the palliative therapy and liver transplantation options for unresectable perihilar cholangiocarcinoma.

Zhang W, Yan LN. Perihilar cholangiocarcinoma: Current therapy. *World J Gastrointest Pathophysiol* 2014; 5(3): 344-354 Available from: URL: http://www.wjgnet.com/2150-5330/full/v5/i3/344.htm DOI: http://dx.doi.org/10.4291/wjgp.v5.i3.344

INTRODUCTION

Cholangiocarcinoma, which is a rare malignant tumor, constitutes less than 1% of all human malignancies[1]. The spectrum of cholangiocarcinoma is divided into three types, according to the anatomical location. Perihilar cholangiocarcinoma (PHC) is the most common type of the malignant tumor accounting for 50%-67% of all cases, followed by distal cholangiocarcinoma (DCCA) and intrahepatic cholangiocarcinoma (ICCA), which account for 27%-42% and 6%-8%, respectively[2,3]. When first described by Klatskin, PHC was commonly called Klatskin tumor[4]. Ben-Menachem summarized that the most common risk factors of PHC were liver flukes, primary sclerosing cholangitis, choledochal cysts, hepatolithiasis and cirrhosis, which account for 10% of the cases[5]. Patients with PHC are usually admitted to the hospital with severe painless jaundice and are diagnosed at an advanced stage, which means a poor prognosis and a shortened life span.

Complete resection is recognized as an effective therapy for many carcinomas. Similarly, resection has long

been demonstrated to be the best option for patients with PHC, and is associated with long-term survival and better quality of life[6]. PHC surgery was previously considered to be a challenge for hepatobiliary surgeons, because of the complex, intimate and variable anatomical relationship of the bile duct and vascular structures[7]. Because of the anatomical characters and the slow progression of the tumor, palliative procedures have been used to treat cancers involving the hepatic hilus, whereas definitive surgery can only be applied to a minority of patients with well-localized lesions[8]. From 1955 to 1973, Longmire collected 63 patients with extrahepatic cholangiocarcinoma (ECCA), and 34 of those patients had lesions that originated near the confluence of the hepatic duct. However, only six patients (18%) were likely candidates for hepatic resection. Guthrie *et al*[9] gathered 107 patients with ECCA divided into two periods, 1980-1985 and 1986-1991. They found that the overall resectablity rate (17%) was similar to that reported in other studies, while the use of percutaneous transhepatic cholangiography decreased and the use of endoscopic retrograde cholangiography increased in the second period. However, palliative treatments had unsatisfactory results and were associated with a high incidence of recurrent cholangitis and jaundice. Furthermore, the palliative approaches did not provide a method for curing the tumors; the techniques only served to relieve the symptoms of biliary obstruction.

With the development of radiology, oncology, liver transplantation and a better understanding of the pathways of tumor spread, surgical methods have recently improved significantly. Radical resection with a microscopically negative margin is believed to be the only way to cure patients with PHC. During recent decades, various surgical innovations and strategies have been introduced to achieve this goal. Currently, left or right hepatic resection, routine caudate lobe resection, lymphadenectomy, vascular resection and portal vein arterialization were promoted to improve outcome in patients with PHC. Nevertheless, for those patients who were not candidates for curative resection, several palliative treatments, such as chemotherapy, radiotherapy and photodynamic therapy, could be used to improve the quality of their life.

SURGERY

Staging and assessment of resectability

For various types of cancers, the American Joint Committee on Cancer (AJCC) TNM staging system is the most useful classification. The latest AJCC edition (7th edition) separates the ECCA into PHC and DCCA, which shows that the two subtypes have their own characteristics in pathology, treatment and prognosis. Based on the primary tumor (T), regional lymph nodes (N) and metastasis (M), the stage group is divided into 0-Ⅳ. Except for the "basic stage", the TNM classification has additional descriptions for residual tumor and histological grade. This classification is usually associated with the histological classification, also known as pathological staging, which is mostly used to stage tumors after surgical resection[10]. However, the majority of experts thought that the classification failed to indicate local respectability of the tumor and to distinguish between various surgical options, which limited the use of the staging system in the preoperative setting[11].

Proposed in the 1970s, the Bismuth-Corlette classification is the most useful stage system for predicting the resectability and for assessing the longitudinal intraductal extension of resection. Four types are classified according to the location and the longitudinal extension of the tumor in the biliary tree. Type Ⅰ lesions involve the common hepatic duct immediately below the confluence; Type Ⅱ lesions involve the hepatic bile duct confluence, that is beyond the confluence; Type Ⅲa and Ⅲb lesions occlude the common hepatic duct and either the right or the left hepatic duct, respectively; and Type Ⅳ lesions involve the confluence and both right and left hepatic ducts[12,13]. In Bismuth's opinion, Types Ⅰ and Ⅱ lesions would require only a local resection of the bile duct with a hepaticojejunostomy reconstruction, whereas the right or left hepatectomy for Type Ⅲa or Ⅲb lesions and hepatectomy plus liver transplantation for Type Ⅳ lesions, could be a contraindication for resection[13]. However, the Bismuth classification fails to describe the radical extension of the cancerous lesion and cannot provide complete information concerning vascular involvement and lymph node involvement, distant metastasis and liver atrophy. Thus, the staging system is primarily used as a convenient guideline for a surgical approach.

Combining the radial and longitudinal extensions of PHC, a preoperative clinical staging system was introduced by Jarnagin and Blumgart at Memorial Sloan-Kettering Cancer Center (MSKCC). This system, which was formally summarized and published in 2001, is also known as the T-staging system , and consists of local tumor extent, biliary duct, portal vein and hepatic lobar atrophy (Table 1)[14,15]. This system could be used to stratify patients preoperatively for the likelihood of respectability and to counsel patients on the potential for an R0 resection. In 2007, Chen *et al*[16] used this staging system to assess 85 patients with PHC. The 1-year survival rates of T1, T2 and T3 patients were 71.8%, 50.8% and 12.9%, respectively; whereas the 3-year survival rates were 34.4%, 18.2% and 0%, respectively[16]. The patients with PHC in the T1 and T2 stages were likely candidates for curative resection, whereas those in the T3 stage could not achieve R0 resection even if they had undergone resection[16]. Another retrospective test in 380 patients showed that the R0 resection rates for T1, T2 and T3 patients were 44.1%, 36.1% and 1.3%, respectively; whereas the median survival was 22.8, 23 and 10.8 mo, respectively[17]. Both surveys demonstrated that the T stage was associated with resectability and long-term survival. Moreover, the MSKCC provided the criteria for unresectable PHC, which included the following: locally

Table 1 Memorial sloan-kettering cancer center classification

Stage	Criteria
T1	Tumor involving biliary confluence ± unilateral extension to second-order biliary radicles.
T2	Tumor involving biliary confluence ± unilateral extension to second-order biliary radicles and ipsilateral portal vein involvement ± ipsilateral hepatic lobar atrophy
T3	Tumor involving biliary confluence + 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 venous involvement

Table 2 Criteria for unresectability[15]

Patient factors
Medically unfit or otherwise unable to tolerate a major operation
Hepatic cirrhosis
Local tumor-related factors
Tumor extension to secondary biliary radicles bilaterally
Encasement or occlusion of the main portal vein proximal to its bifurcation
Atrophy of one hepatic lobe with contralateral portal vein branch encasement or occlusion
Atrophy of one hepatic lobe with contralateral tumor extension to secondary biliary radicles
Unilateral tumor extension to secondary biliary radicles with contralateral portal vein branch
encasement or occlusion
Metastatic disease
Histologically proven metastases to N2 lymph nodes[1]
Lung, liver, or peritoneal metastases

[1]Metastatic disease to peripancreatic, periduodenal, celiac, superior mesenteric, or posterior pancreaticoduodenal lymph nodes was considered to represent disease not amenable to a potentially curative resection. By contrast, metastatic disease to cystic duct, pericholedochal, hilar, or portal lymph nodes (*i.e.*, within the hepatoduodenal ligament) did not necessarily constitute unresectability.

advanced tumor extending bilaterally to the secondary biliary radicles, unilateral sectional bile ducts with contralateral portal vein branch involvement, encasement or occlusion of the primary portal vein proximal to its bifurcation, and atrophy of one hepatic lobe with contralateral tumor extension to sectional bile ducts (Table 2)[15].

A recent report indicated that a new system was designed by the international cholangiocarcinoma group, which incorporated the size of the tumor, the extent of the disease in the biliary system, the involvement of the hepatic artery and portal vein, the involvement of lymph nodes, distant metastases, and the volume of the putative remnant liver after resection[10]. Despite its comprehensiveness, this new classification must be validated and accepted.

We searched the key words "hilar cholangiocarcinoma", "Klatskin tumor" and "resection" using Pubmed and Medline, and we summarized the respectability and the outcomes from different institutions in different periods. The results of the surgical treatment are shown in Table 3[2,3,8,15,17-51]. Although the data were not fully calculated and were derived from tertiary referral centers, the number of patients with PHC who had undergone the resection was small, and only few large institutions contained more than 300 cases[42,50,51]. These findings attested to the rarity of this disease; additionally, these results indicated that the majority of patients lost the opportunity to undergo a curative operation when diagnosed, and therefore, these patients were not counted in the total number of study participants. Table 3 shows that the resectability rate was significantly variable, ranging from 28% to 95%, and that the curative resection rate ranged from 14% to 95%. This wide variability may be attributed to the differences in the sample content, the broad range of dates for inclusion, the characteristics of patients in different geographical areas, the methods of patient selection and the preoperative techniques in these studies.

Surgical procedures and strategies

In several reports, the surgical procedures were as follows: (1) preoperative biliary drainage was conducted to reduce the serum bilirubin concentration below 2 mg/dL; (2) preoperative percutaneous transhepatic portal embolization was performed when the volume of the liver remnant was estimated to be less than 40%; (3) the operative procedures for hilar resection were determined and planned using multidetector row computed tomography (MRCT); (4) the skeletonization of the portal vein and hepatic artery was performed using nodal clearance around the head of the pancreas; (5) portal vein resection and reconstruction were conducted before hepatic dissection if necessary; (6) frozen sections of the resected margins of the bile duct were investigated; and (7) lymph nodes in the hepatoduodenal ligament, around the head of pancreas and around the common hepatic artery were completely removed, whereas lymph nodes in the para-aortic region were removed, if possible, with a curative resection[44]. In other institutions, the surgical procedure included the hepatic artery resection, reconstruction and arterioportal shunt.

Obstructive jaundice, which is the most common symptom in patients with PHC, may increase the in-hospital mortality by 10% and is associated with many complications, such as bacterial translocation, malnutrition, renal insufficiency and postoperative liver dysfunction[52,53]. To avoid the risk of hepatic resection, preoperative biliary drainage (PBD) is recommended by many surgical teams. Percutaneous transhepatic biliary drainage (PTBD) had previously been widely used; however, several prospective randomized studies showed

Table 3 Results of surgical resection for perihilar cholangiocarcinoma

Ref.	Published year	Resections	Resectablity (%)	Negative margin (%)	Liver resection (%)	Morbidity	Mortality	5-yr survival rate (%)
Hadjis *et al*[18]	1990	27	NA	56	60	NA	7	22
Nakeeb *et al*[2]	1996	109	56	26	14	47	4	11
Su *et al*[19]	1996	49	28	49	57	47	10	15
Klempnauer *et al*[20]	1997	151	45	77	77	NA	10	28
Miyazaki *et al*[21]	1998	76	NA	71	86	34	13	26
Neuhaus *et al*[22]	1999	80	NA	61	85	55	8	22
Kosuge *et al*[8]	1999	65	73	52	80	37	9	33
Gerhards *et al*[23]	2000	112	NA	14	29	65	18	NA
Nimura *et al*[24]	2000	142	80	61	90	49	9	26
Todoroki *et al*[25]	2000	101	89	14	58	14	4	28
Jarnagin *et al*[15]	2001	80	50	78	78	64	10	26
Kawarada *et al*[27]	2002	65	89	64	75	28	2.3	26
Capussotti *et al*[26]	2002	36	NA	89	83	47	3	27
Kawasaki *et al*[28]	2003	79	75	68	87	14	1.3	22
Seyama *et al*[29]	2003	87	94	64	67	43	0	40
Rea *et al*[32]	2004	46	NA	80	100	52	9	26
Kondo *et al*[31]	2004	40	95	95	65	48	0	NA
I.Jitsma *et al*[30]	2004	42	NA	65	100	76	12	19
Hemming *et al*[33]	2005	53	50	80	98	40	9	35
Jarnagin *et al*[34]	2005	106	70	77	82	62	8	NA
Dinant *et al*[35]	2006	99	NA	31	38	66	15	27
DeOliveira *et al*[3]	2007	173	62	19	20	61	5	10
Ito *et al*[36]	2008	38	55	63	53	32	0	33
Konstadoulakis *et al*[37]	2008	59	81	68.6	86.4	25.5	6.8	34.9
Igami *et al*[41]	2010	298	70	74	98	43	2	42
Hirano *et al*[40]	2010	146	NA	87	87	44	3.4	35.5
Lee *et al*[42]	2010	302	86	70.9	89	43	1.7	32.5
Unno *et al*[44]	2010	125	NA	63.2	100	48.7	8	34.7
Ercolani *et al*[38]	2010	51	49.6	72.5	98	51	10	34.1
Shimizu *et al*[43]	2010	224	NA	69.1	78	47.6	10.7	30.3
Giuliante *et al*[39]	2010	43	29	77	93	52.5	6.9	36.1
Regimbeau *et al*[45]	2011	56	NA	76.9	100	72	8	NA
Young *et al*[48]	2012	83	92	42.2	93	62.7	7	20
Saxena *et al*[47]	2012	54	64	64.3	42	45.2	2.4	24
Ribero *et al*[46]	2012	82	NA	81.7	91.5	64.6	9.7	28
De Jong *et al*[50]	2012	305	NA	64.2	73	NA	10.6	20.2
Matsuo *et al*[17]	2012	157	78	76	90	59.2	7.6	37.5
Cheng *et al*[49]	2012	176	34	78.4	97	26.3	2.9	13.5
Nagino *et al*[51]	2013	574	76.1	76.5	96.7	57.3	4.7	32.5

NA: Not applicable.

that PTBD had no benefit in postoperative morbidity and mortality but increased potential risks, such as vascular injury, infectious complications and tumor seeding metastasis[54-56]. Currently, endoscopic nasobiliary drainage (ENBD) is performed instead of PTBD because of fewer complications and better outcomes. More recently, the Nagoya Institute demonstrated that unilateral ENBD of the future remnant lobe(s) exhibited a high success rate as an effective and suitable PBD method even in BC type Ⅲ to Ⅳ lesions[57]. To avoid the postoperative liver dysfunction resulting from extended hepatic resection, many institutions have promoted portal vein embolization (PVE) to increase volume of the future liver remnant (FLR). In several cautious surgical centers, when the FLR was 40% or less of the total liver volume, PVE was performed because the serum bilirubin level had decreased to less than 10 mg/dL[41,46]. Subsequently, surgery was performed after 2-4 wk of liver hypertrophy due to clonal expansion and cellular response[58].

When determining the surgical approach, the local excision, hepatectomy, and extended hepatectomy with or without caudate resection should be considered. In the Bismuth's opinion, Bismuth Type Ⅰ and Ⅱ would require only a local resection. Recently, bile duct resection alone without hepatectomy has been largely abandoned in favor of a more aggressive approach. Capussotti *et al*[59] conducted a systematic review of the effect of local resection compared with hepatectomy. In the pathologic aspect, the isolated bile duct cannot be adequately resected, because of the following: the necessity for wide surgical margins; neoplastic extension along the perineural sheaths and segment 1 neoplastic invasion. From another perspective, the R0 resection rate was higher after combined liver resection, although, in the earlier years of its application, local resection could be associated with fewer complications and shorter lengths of hospital stay[15,21,35]. In conclusion, according to this systematic review, local resection should only be scheduled for small papillary Klatskin tumors without bile duct confluence involvement confined to the bile duct wall[59]. Because

of the rarity and the advanced stage of the disease at the time of diagnosis, a local resection was rarely performed.

Despite the incomplete accuracy, the Bismuth classification initiated the idea of wider resection for PHC[13]. Table 3 shows that liver resection rates increased from 14% to 100% with an increased R0 resection rate. The common liver resection strategies are as follows: right or left hepatectomy (resection of hepatic segments 5, 6, 7, 8 or 2, 3, 4 ± 1), right or left hepatic trisectionectomy, also called extended right or left hepatectomy (resection of hepatic segments 4, 5, 6, 7, 8 or 2, 3, 4, 5, 8 ± 1), and central hepatectomy. Bisectionectomy or more was defined as a major hepatectomy; sectionectomy or less was defined as a minor hepatectomy[38]. Currently, for those patients with Bismuth type Ⅰ and Ⅱ, the right hepatectomy with caudate lobectomy was recommended, which has been demonstrated to decrease the rate of recurrence[29]. However, for those patients with Bismuth types Ⅲ and Ⅳ lesions, the approaches varied in different institutions. Recently, Cheng *et al*[49] reported 171 patients with PHC of Bismuth types Ⅲ and Ⅳ lesions. For Bismuth Type Ⅲ lesions, right, left or central hepatectomy with caudate lobectomy was performed. For Bismuth Ⅳ lesions, the right or left hepatectomy or extended right or left hepatectomy with caudate lobectomy was conducted to increase the negative margin rates. The choice of surgical side may depend on the predominance of the tumor; however, the right trisectionectomy is indicated for centrally located tumors because of the length of each hepatic duct, the location of the hilar common bile duct in the hepatoduodenal ligament, the ease of complete caudate lobectomy and portal vein reconstruction, and the frequent involvement of the right hepatic artery[7,28]. The left hepatectomy is considered to be a more complicated procedure than the right hepatectomy and requires greater skill, especially in cases involving portal vein resection and reconstruction. Moreover, preserving the right hepatic artery and the right portal vein could be an oncological problem with left or extended left resection, which could increase the tumor cell dissemination. Therefore, the rate of left hepatectomies is approximately 25%-30% of all resections[60]. In the study by Shimizu *et al*[43], the R0 resection was achieved in all 7 patients who underwent right trisectionectomy, but in only 8 (61.5%) of 13 patients who underwent left trisectionectomy. This finding suggests that a more extended resection from the right side, but not from the left side, may provide greater potential for curability. However, several authors believed that the left extended hepatectomy could achieve the same result. Nagino *et al*[51] analyzed the patients with PHC who underwent surgery and compared the surgical strategies in different periods (Table 4). From their experience, the incidence of left hepatic trisectionectomies gradually increased while the incidence of central hepatectomies decreased. Totally, the left or extended left hepatectomy represented nearly 55% of all of the resections performed on patients with PHC.

Nimura *et al*[61] introduced the concept of routine caudate lobectomy (CL). Bilateral biliary branches of the caudate lobe are confluent with the right hepatic duct, the left hepatic duct, the confluence of these and the right posterior hepatic duct. Therefore, the caudate lobe is usually involved in PHC in 40% to 98% of patients, which indicates a need for CL[61-63]. Moreover, routine CL combined with resection had high curative resectablity rates and increased the likelihood of long-term survival for patients with advanced stage PHC[49]. Similarly, Kow *et al*[64] showed that the patients with CL had a significantly better overall survival rate of 64.0 mo compared to the survival rate of 34.6 mo in type Ⅲ PHC patients in the group without CL. Although mechanisms for CL have not been established, the outcome remains optimistic while undertaking CL in PHC.

A major hepatectomy combined with pancreatoduodenectomy, for example, hepatopancreatoduodenectomy (HPD), was routinely used in the PHC surgery in several institutions. This procedure occupied 12.9% of the total surgery cases, and was indicated in the following cases: (1) diffusely infiltrating tumors of the entire extrahepatic bile duct; and (2) downward superficial spreading, or bulky nodal metastases of the pancreatoduodenal region (Table 4)[65]. Therefore, HPB provides an important method for treating spreading unresectable cholangiocarcinoma; thus, it is now the fourth standard procedure following hepatectomy, bile duct resection, and pancreatoduodenectomy[66].

In several high-volume samples, PHC was frequently reported to metastasize via the lymphatics in 24% to 75% of the patients[42,51]. Moreover, many authors had demonstrated that lymph node metastasis had a negative impact on survival in PHC[3,28,29,31,33,42,51]. Thereafter, lymphadenectomy played a crucial role in the outcome of patients with PHC. However, the 5-year survival rate is related to the location of the metastasis of the lymph node. Therefore, lymph node metastasis that is confined to the hepatic pedicle or the hepatoduodenal ligament is not a reason for abandoning resection. The tumor positive lymph nodes along the common hepatic artery or celiac axis are usually considered a contraindication for resection[7]. Kitagawa *et al*[67] showed that, in 110 patients after resection of PHC, there was a 5-year survival rate of 31%, if the lymph nodes were negative. However, in patients suffering from a local or a para-aortic lymph node infiltration, the 5-year survival rates were 15% and 12%, respectively. Interestingly, in the same report, 12% of the patients with positive para-aortic lymph nodes who lived more than 5 years were found to have macroscopically negative nodes in surgery[67]. Although the routine lymph node dissection beyond the hepatoduodenal ligament is not generally recommended, several authors still believe that lymph node dissection is beneficial.

Due to the intimate relationship between the bile duct and vessels, PHC could usually infiltrate the portal vein and hepatic artery. The indication for portal vein

Table 4 Surgery performed according to the time period[51] *n* (%)

	Total	Time period				*P*
		Earlier period		Later period		
		1997-1990	1991-2000	2001-2005	2006-2010	
Number of patients resected	574	72	116	168	218	
Resectability	574/754 (76.1)	72/93 (77.4)	116/148 (78.4)	168/216 (77.8)	218/297 (73.4)	0.406
Type of hepatectomy[1]						< 0.001
S1,4,5,6,7,8	43 (7.5)	5 (6.9)	11 (9.5)	4 (2.4)	23 (10.6)	
S1,5,6,7,8	177 (30.8)	17 (23.6)	40 (34.5)	53 (31.5)	67 (30.7)	
S1,2,3,4,5,8,	110 (19.2)	4 (5.6)	12 (10.3)	29 (17.3)	65 (29.8)	
S1,2,3,4	187 (32.6)	27 (37.5)	35 (30.2)	68 (40.5)	57 (26.1)	
S1,4,5,8/S1,5,8/S1,4/S1	38 (6.6)	13 (18.1)	10 (8.6)	11 (6.5)	4 (1.8)	
Without hepatectomy	19 (3.3)	6 (8.3)	8 (6.9)	3 (1.8)	2 (0.9)	
Combined resection						
Pancreatoduodenectomy	74 (12.9)	9 (12.5)	13 (11.2)	20 (11.9)	32 (14.7)	0.553
Portal vein resection	206 (35.9)	23 (31.9)	36 (31.0)	58 (34.5)	89 (40.8)	0.116
Wedge resection	36	15	6	10	5	
Segmental resection	170	8	30	48	84	
Hepatic artery resection	76 (13.2)	0	5 (4.3)	25 (14.9)	46 (21.1)	< 0.001
Operative time, min[2]	668 ± 134	664 ± 162	787 ± 170	675 ± 145	605 ± 134	< 0.001
Blood loss, mL[2]	2491 ± 2156	4414 ± 2791	3773 ± 3024	1898 ± 1268	1768 ± 1130	< 0.001
Homologous blood transfusion	271 (47.2)	68 (94.4)	93 (80.2)	46 (27.4)	64 (29.4)	< 0.001

Homologous blood includes packed red blood cell and fresh-frozen plasma. Note that P indicates the statistical difference between the earlier period (1977-2000) and the later period (2001-2010). [1]Expressed as Couinaud's hepatic segments resected; [2]Excluding 19 patients who did not undergo hepatectomy.

resection (PVR) and reconstruction for PHC is controversial. Previously, tumors involving the portal vein were considered unresectable. However, more recently, several surgeons have advocated this approach and its clinical benefit has been validated in many studies[22,28,29,31,33,42,50]. de Jong *et al*[50] reported the results of the analysis of an international, multicenter database from seven major hepatobiliary centers. They found that the PVR for PHC was associated with a greater risk for 30-d and 90-d perioperative mortality. Nevertheless, they thought that PVR should be undertaken, when necessary, to extirpate all of the disease because of its association with long-term survival in several patients with PHC[50]. Similarly, Nanigo recommended that PVR should be performed only when the vessel adhered to and could not be freed from the tumor during the skeletonization resection of the hepatoduodenal ligament and that PVR should not be performed as a routine procedure because it lacked scientific validation[68]. Because of the short distance between the tumor and the portal vein, Neuhaus *et al*[22] proposed a "no-touch" concept in 1999 and recommended routine PVR to achieve a wider distal radicality. Additionally, Neuhaus *et al*[69] proposed a survey to compare the effect of the "no-touch" resection with the traditional curative resection. The 5-year survival rate was significantly higher in the "no-touch" group at 58% compared to 29% in the traditional curative resection group ($P = 0.021$). However, this new technique has not been accepted by many institutions because it lacks scientific validation and more random studies are warranted for additional investigation.

In earlier reports, few institutions proposed the surgical strategy of hepatic resection combined with hepatic artery resection in patients with advanced PHC. In small samples, the outcome and survival rates were disappointing. Therefore, many authors did not recommend this surgical strategy[43,62,70]. Shimizu *et al*[43] showed that all of the nine patients undergoing left-sided hepatectomy combined with hepatic artery resection lived less than 3 years, and they considered that the hepatic artery resection was a primary prognostic factor (RR = 3.063; 95%CI: 1.289-7.282). However, in 2010, the Nagoya Institute reported their experiences with major hepatectomies with simultaneous resections and reconstructions of the portal vein and hepatic artery; the investigators showed that the challenging surgery could be performed with an acceptable mortality rate of 2% and offered a better likelihood of long-term survival with a 5-year survival rate of 30%[71]. Currently, the number of patients undergoing hepatic artery resection has been increasing (Table 4). In the institute's published data of 107 patients, the majority of patients (95%) underwent left-sided hepatectomies, of which 59% were left trisectionectomies and 36% were left hepatectomies. The overall mortality rate was 2.8% and the 5-year survival rate was 34.1%. The resected hepatic arteries were reconstructed primarily by end-to-end anastomosis, with an arterioportal shunt or an interposition graft using the radial artery or great saphenous vein[68]. For those patients who are unable to undergo hepatic artery reconstruction after resection, portal vein arterialization (PVA) could be a new approach. Using this method, adequate oxygen delivery to hepatocytes and biliary ducts can be assured. Moreover, several animal experiments showed that PVA could promote hepatic cell proliferation and enhance liver regeneration after extended hepatic resection[72]. The clini-

cal significance of hepatic artery resection is debatable, yet also promising and encouraging.

Morbidity and mortality

In Table 3, we summarize the morbidity and mortality which show significant variations, ranging from 14% to 76% and from 0% to 18%, respectively. Sano *et al*[73] defined the complications as major when they resulted in organ failure or required another surgery or interventional radiology, such as liver failure, lung failure and renal failure[51,73]. Complications that were classified as minor include pleural effusion necessitating thoracocentesis, wound infection, intra-abdominal infection with positive culture of the drainage fluid, delayed gastric emptying, anastomotic leakage, clinically silent pancreatic fistula with amylase-rich serous fluid or contaminated fluid with positive culture, and bile leakage from the raw surface of the liver healing spontaneously or responding to conservative management[73]. The most common complications observed in most institutions were infective complications, especially during earlier years of the use of these procedures, representing 50% or more of the observed complications[3,15,36]. Nagiono *et al*[51] compared the complications between the earlier years and the more recent years, and they demonstrated that the incidence of grade C liver failure, which is clinically serious, decreased markedly from 18.2% from 1977 to 1990 to 3.2% from 2006 to 2010. Wound sepsis was the second most common complication, followed by intra-abdominal abscess and bile leakage[51].

The operative mortality included all in-hospital deaths as defined by Sano. All postoperative complications that affected the outcome or lengthened the hospital stay were considered. Death may be associated with acute liver failure after extended right hepatectomy and combined portal vein resection, and sepsis with multiorgan failure[45]. Overall, these extended liver as well as vascular resections were found to be significant predictors of increased mortality[23]. In addition to liver function, operative time and blood loss may be associated with mortality[51]. Several reports have demonstrated that preoperative portal vein embolization may decrease mortality even with extended hepatectomy[73].

Outcomes and recurrence

The average 5-year survival rates after resection for PHC range from 11% to 42% (Table 3). Factors associated with favorable outcome include the following: R0 resection, no lymph node metastasis, absence of perineural and perivascular invasion, and well-differentiated histological grade. Complete resection with negative histologic margins is the only modifiable factor and, for that reason, the primary aim of surgical therapy. Recently, several reports demonstrated that patients undergoing R1 resection (microscopically positive margin) had a longer overall survival rate than patients with unresectable PHC[36,74]. Moreover, patients undergoing R0 resections with a margin less than 5 mm had the same survival rate as those patients undergoing R1 resections[29]. The surgeons were encouraged to perform more aggressive surgery to achieve a better outcome.

Few studies have analyzed recurrence patterns and time to recurrence in patients with PHC. In several reports, tumor recurrence rates can be as high as 50% to 76%, and the median time to recurrence rates has been reported to be 12 to 43 mo[36,47,75,76]. The most common site of recurrence is a local site, followed by the liver, lymph node, peritoneum and other organs. Only histologic grade was associated with recurrence-free survival[47]. Generally, the patients with recurrent disease are not candidates for curative therapy and can only receive adjuvant therapy to improve long-term outcome.

ORTHOTOPIC LIVER TRANSPLANTATION

Theoretically, orthotopic liver transplantation (OLT) offers the advantage of the resection of all of the structures that may be affected by tumor, for example, the portal vein, bilateral hepatic ducts and atrophic liver lobes. Compared to surgical resection, OLT has several advantages: (1) patients with Bismuth Ⅳ type lesions and peripheral vascular lesions cannot undergo resection; (2) patients with PHC arising from primary sclerosing cholangitis (PSC) will tolerate resection poorly because of the underlying liver impairment; (3) dissection in the hepatic hilum has the potential for causing spillage, which is an adverse prognostic factor; and (4) a clear circumferential margin is usually not achievable, which might increase the recurrence rates of PHC[77]. However, in the early years of the application of this procedure, the results were disappointing. The Cincinnati Transplant Tumor Registry collected global data between 1968 and 1997. The 1-, 2-, and 5-year survival rates were 72%, 48%, and 23%, respectively. Eighty four percent of the patients had a recurrence within 2 years of transplantation[78]. This undesirable result may have been associated with the unselected patients who had distant metastasis. Despite this finding, PHC was considered to be a relative contraindication to OLT due to the lack of organs. Interestingly, several investigations found that those patients with negative margins in transplantation and the absence of regional lymph node metastases had a better survival rate. Moreover, 22% of the patients receiving radiotherapy and chemotherapy alone had a 5-year survival, which inspired several surgeons to explore a new OLT approach for PHC.

From 1987 to 2000, Miyazaki *et al*[70] collected 17 patients who were treated with systemic chemotherapy and intraluminal bile duct irradiation as they awaited liver transplantation. Eleven patients underwent liver transplantation, and until 2000, five patients were alive without evidence of tumor recurrence with a median follow-up of 7.5 years (range, 2.8-14.5 years). In 1994, the Mayo Clinic developed a protocol employing preoperative chemoradiation therapy followed by liver transplantation, which showed encouraging results. Currently,

Table 5 Criteria for neoadjuvant therapy and liver transplantation[82]

Diagnosis of cholangiocarcinoma
Transcatheter biopsy or brush cytology
CA-19.9 > 100 mg/mL and/or a mass on cross-sectional imaging with a malignant appearing stricture on cholangiography
Biliary ploidy by FISH with a malignant appearing stricture on cholangiography
Unresectable tumor above cystic duct
Pancreatoduodenectomy for microscopic involvement of the common bile duct
Resectable cholangiocarcinoma arising in PSC
Radial tumor diameter ≤ 3 cm
Absence of intra- and extrahepatic metastases
Candidate for liver transplantation

PSC: Primary sclerosing cholangitis.

according to the Mayo Clinic protocol, patients receive EBRT (a target dose of 4500 cGy) with protracted venous infusion of 5-FU (225 mg/m^2 per day). Following this treatment, transcatheter iridium-192 brachytherapy (a target dose of 2000 cGy) is administered. Subsequently, the patients receive oral capecitabine (1000 mg/m^2 per day in two divided doses) until the time of OLT. Importantly, a staging laparotomy is performed on all of the patients before OLT to rule out metastatic disease. Only the patients with negative staging operations are eligible for transplantation[79]. Although there is a high dropout rate as patients await liver transplantation, the 5-year survival rate could achieve approximately 65% to 70%. However, the majority of patients undertaking OLT were diagnosed with PSC, and only 58% patients had histologically proven cancer which limited the use of OLT[80].

In 1996, Pichlmayr *et al*[81] proposed the indications for OLT in patients with PHC as follows: (1) unresectablity in presumed UICC stage Ⅱ confirmed by laparotomy; (2) status postresection with the intention for R0 with R or R2 positive resection margins due to advanced central tumor infiltration; and (3) local intrahepatic recurrence. After additional exploration and analysis of PHC, the Mayo Clinic proposed their criteria for neoadjuvant therapy and liver transplantation[82] (Table 5). These types of patients would be excluded if they had the following: (1) intrahepatic cholangiocarcinoma; (2) uncontrolled infection; (3) prior radiation or chemotherapy; (4) prior biliary resection or attempted resection; (5) intrahepatic metastases; (6) evidence of extrahepatic disease; (7) history of other malignancy within 5 years; and (8) transperitoneal biopsy[82]. Although the Mayo Clinic protocol has been accepted in the majority of institutions, the role of OLT requires additional substantial evidence and data confirmation from multiple institutions.

REFERENCES

1 **Siegel R**, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013; **63**: 11-30 [PMID: 23335087]
2 **Nakeeb A**, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, Hruban RH, Lillemoe KD, Yeo CJ, Cameron JL. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. *Ann Surg* 1996; **224**: 463-473; discussion 473-475 [PMID: 8857851]
3 **DeOliveira ML**, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, Choti MA, Yeo CJ, Schulick RD. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007; **245**: 755-762 [PMID: 17457168 DOI: 10.1097/01.sla.0000251366.62632.d3]
4 **Klatskin G**. Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis. an unusual tumor with distinctive clinical and pathological features. *Am J Med* 1965; **38**: 241-256 [PMID: 14256720]
5 **Ben-Menachem T**. Risk factors for cholangiocarcinoma. *Eur J Gastroenterol Hepatol* 2007; **19**: 615-617 [PMID: 17625428 DOI: 10.1097/MEG.0b013e328224b935]
6 **Launois B**, Campion JP, Brissot P, Gosselin M. Carcinoma of the hepatic hilus. Surgical management and the case for resection. *Ann Surg* 1979; **190**: 151-157 [PMID: 223508]
7 **Ramos E**. Principles of surgical resection in hilar cholangiocarcinoma. *World J Gastrointest Oncol* 2013; **5**: 139-146 [PMID: 23919108 DOI: 10.4251/wjgo.v5.i7.139]
8 **Kosuge T**, Yamamoto J, Shimada K, Yamasaki S, Makuuchi M. Improved surgical results for hilar cholangiocarcinoma with procedures including major hepatic resection. *Ann Surg* 1999; **230**: 663-671 [PMID: 10561090]
9 **Guthrie CM**, Haddock G, De Beaux AC, Garden OJ, Carter DC. Changing trends in the management of extrahepatic cholangiocarcinoma. *Br J Surg* 1993; **80**: 1434-1439 [PMID: 7504567]
10 **Deoliveira ML**, Schulick RD, Nimura Y, Rosen C, Gores G, Neuhaus P, Clavien PA. New staging system and a registry for perihilar cholangiocarcinoma. *Hepatology* 2011; **53**: 1363-1371 [PMID: 21480336 DOI: 10.1002/hep.24227]
11 **de Jong MC**, Hong SM, Augustine MM, Goggins MG, Wolfgang CL, Hirose K, Schulick RD, Choti MA, Anders RA, Pawlik TM. Hilar cholangiocarcinoma: tumor depth as a predictor of outcome. *Arch Surg* 2011; **146**: 697-703 [PMID: 21690446 DOI: 10.1001/archsurg.2011.122]
12 **Bismuth H**, Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. *Surg Gynecol Obstet* 1975; **140**: 170-178 [PMID: 1079096]
13 **Bismuth H**, Nakache R, Diamond T. Management strategies in resection for hilar cholangiocarcinoma. *Ann Surg* 1992; **215**: 31-38 [PMID: 1309988]
14 **Burke EC**, Jarnagin WR, Hochwald SN, Pisters PW, Fong Y, Blumgart LH. Hilar Cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. *Ann Surg* 1998; **228**: 385-394 [PMID: 9742921]
15 **Jarnagin WR**, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BS J, Youssef BA M, Klimstra D, Blumgart LH. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg* 2001; **234**: 507-517; discussion 517-519 [PMID: 11573044]

16 **Chen RF**, Li ZH, Zhou JJ, Wang J, Chen JS, Lin Q, Tang QB, Peng NF, Jiang ZP, Zhou QB. Preoperative evaluation with T-staging system for hilar cholangiocarcinoma. *World J Gastroenterol* 2007; **13**: 5754-5759 [PMID: 17963304]

17 **Matsuo K**, Rocha FG, Ito K, D'Angelica MI, Allen PJ, Fong Y, Dematteo RP, Gonen M, Endo I, Jarnagin WR. The Blumgart preoperative staging system for hilar cholangiocarcinoma: analysis of resectability and outcomes in 380 patients. *J Am Coll Surg* 2012; **215**: 343-355 [PMID: 22749003 DOI: 10.1016/j.jamcollsurg.2012.05.025]

18 **Hadjis NS**, Blenkharn JI, Alexander N, Benjamin IS, Blumgart LH. Outcome of radical surgery in hilar cholangiocarcinoma. *Surgery* 1990; **107**: 597-604 [PMID: 2162082]

19 **Su CH**, Tsay SH, Wu CC, Shyr YM, King KL, Lee CH, Lui WY, Liu TJ, P'eng FK. Factors influencing postoperative morbidity, mortality, and survival after resection for hilar cholangiocarcinoma. *Ann Surg* 1996; **223**: 384-394 [PMID: 8633917]

20 **Klempnauer J**, Ridder GJ, von Wasielewski R, Werner M, Weimann A, Pichlmayr R. Resectional surgery of hilar cholangiocarcinoma: a multivariate analysis of prognostic factors. *J Clin Oncol* 1997; **15**: 947-954 [PMID: 9060532]

21 **Miyazaki M**, Ito H, Nakagawa K, Ambiru S, Shimizu H, Shimizu Y, Kato A, Nakamura S, Omoto H, Nakajima N, Kimura F, Suwa T. Aggressive surgical approaches to hilar cholangiocarcinoma: hepatic or local resection? *Surgery* 1998; **123**: 131-136 [PMID: 9481397]

22 **Neuhaus P**, Jonas S, Bechstein WO, Lohmann R, Radke C, Kling N, Wex C, Lobeck H, Hintze R. Extended resections for hilar cholangiocarcinoma. *Ann Surg* 1999; **230**: 808-818; discussion 819 [PMID: 10615936]

23 **Gerhards MF**, van Gulik TM, de Wit LT, Obertop H, Gouma DJ. Evaluation of morbidity and mortality after resection for hilar cholangiocarcinoma--a single center experience. *Surgery* 2000; **127**: 395-404 [PMID: 10776430]

24 **Nimura Y**, Kamiya J, Kondo S, Nagino M, Uesaka K, Oda K, Sano T, Yamamoto H, Hayakawa N. Aggressive preoperative management and extended surgery for hilar cholangiocarcinoma: Nagoya experience. *J Hepatobiliary Pancreat Surg* 2000; **7**: 155-162 [PMID: 10982608 DOI: 10.1007/s005340000070155.534]

25 **Todoroki T**, Kawamoto T, Koike N, Takahashi H, Yoshida S, Kashiwagi H, Takada Y, Otsuka M, Fukao K. Radical resection of hilar bile duct carcinoma and predictors of survival. *Br J Surg* 2000; **87**: 306-313 [PMID: 10718799 DOI: 10.1046/j.1365-2168.2000.01343.x]

26 **Capussotti L**, Muratore A, Polastri R, Ferrero A, Massucco P. Liver resection for hilar cholangiocarcinoma: in-hospital mortality and longterm survival. *J Am Coll Surg* 2002; **195**: 641-647 [PMID: 12437251]

27 **Kawarada Y**, Das BC, Naganuma T, Tabata M, Taoka H. Surgical treatment of hilar bile duct carcinoma: experience with 25 consecutive hepatectomies. *J Gastrointest Surg* 2002; **6**: 617-624 [PMID: 12127130]

28 **Kawasaki S**, Imamura H, Kobayashi A, Noike T, Miwa S, Miyagawa S. Results of surgical resection for patients with hilar bile duct cancer: application of extended hepatectomy after biliary drainage and hemihepatic portal vein embolization. *Ann Surg* 2003; **238**: 84-92 [PMID: 12832969 DOI: 10.1097/01.sla.0000074984.83031.02]

29 **Seyama Y**, Kubota K, Sano K, Noie T, Takayama T, Kosuge T, Makuuchi M. Long-term outcome of extended hemihepatectomy for hilar bile duct cancer with no mortality and high survival rate. *Ann Surg* 2003; **238**: 73-83 [PMID: 12832968 DOI: 10.1097/01.sla.0000074960.55004.72]

30 **IJitsma AJ**, Appeltans BM, de Jong KP, Porte RJ, Peeters PM, Slooff MJ. Extrahepatic bile duct resection in combination with liver resection for hilar cholangiocarcinoma: a report of 42 cases. *J Gastrointest Surg* 2004; **8**: 686-694 [PMID: 15358329 DOI: 10.1016/j.gassur.2004.04.006]

31 **Kondo S**, Hirano S, Ambo Y, Tanaka E, Okushiba S, Morikawa T, Katoh H. Forty consecutive resections of hilar cholangiocarcinoma with no postoperative mortality and no positive ductal margins: results of a prospective study. *Ann Surg* 2004; **240**: 95-101 [PMID: 15213624]

32 **Rea DJ**, Munoz-Juarez M, Farnell MB, Donohue JH, Que FG, Crownhart B, Larson D, Nagorney DM. Major hepatic resection for hilar cholangiocarcinoma: analysis of 46 patients. *Arch Surg* 2004; **139**: 514-523; discussion 523-525 [PMID: 15136352 DOI: 10.1001/archsurg.139.5.514]

33 **Hemming AW**, Reed AI, Fujita S, Foley DP, Howard RJ. Surgical management of hilar cholangiocarcinoma. *Ann Surg* 2005; **241**: 693-699; discussion 693-699 [PMID: 15849505]

34 **Jarnagin WR**, Bowne W, Klimstra DS, Ben-Porat L, Roggin K, Cymes K, Fong Y, DeMatteo RP, D'Angelica M, Koea J, Blumgart LH. Papillary phenotype confers improved survival after resection of hilar cholangiocarcinoma. *Ann Surg* 2005; **241**: 703-712; discussion 712-714 [PMID: 15849506]

35 **Dinant S**, Gerhards MF, Rauws EA, Busch OR, Gouma DJ, van Gulik TM. Improved outcome of resection of hilar cholangiocarcinoma (Klatskin tumor). *Ann Surg Oncol* 2006; **13**: 872-880 [PMID: 16614876 DOI: 10.1245/aso.2006.05.053]

36 **Ito F**, Agni R, Rettammel RJ, Been MJ, Cho CS, Mahvi DM, Rikkers LF, Weber SM. Resection of hilar cholangiocarcinoma: concomitant liver resection decreases hepatic recurrence. *Ann Surg* 2008; **248**: 273-279 [PMID: 18650638 DOI: 10.1097/SLA.0b013e31817f2bfd]

37 **Konstadoulakis MM**, Roayaie S, Gomatos IP, Labow D, Fiel MI, Miller CM, Schwartz ME. Aggressive surgical resection for hilar cholangiocarcinoma: is it justified? Audit of a single center's experience. *Am J Surg* 2008; **196**: 160-169 [PMID: 18466862 DOI: 10.1016/j.amjsurg.2007.07.033]

38 **Ercolani G**, Zanello M, Grazi GL, Cescon M, Ravaioli M, Del Gaudio M, Vetrone G, Cucchetti A, Brandi G, Ramacciato G, Pinna AD. Changes in the surgical approach to hilar cholangiocarcinoma during an 18-year period in a Western single center. *J Hepatobiliary Pancreat Sci* 2010; **17**: 329-337 [PMID: 20464563 DOI: 10.1007/s00534-009-0249-5]

39 **Giuliante F**, Ardito F, Vellone M, Nuzzo G. Liver resections for hilar cholangiocarcinoma. *Eur Rev Med Pharmacol Sci* 2010; **14**: 368-370 [PMID: 20496550]

40 **Hirano S**, Kondo S, Tanaka E, Shichinohe T, Tsuchikawa T, Kato K, Matsumoto J, Kawasaki R. Outcome of surgical treatment of hilar cholangiocarcinoma: a special reference to postoperative morbidity and mortality. *J Hepatobiliary Pancreat Sci* 2010; **17**: 455-462 [PMID: 19820891 DOI: 10.1007/s00534-009-0208-1]

41 **Igami T**, Nishio H, Ebata T, Yokoyama Y, Sugawara G, Nimura Y, Nagino M. Surgical treatment of hilar cholangiocarcinoma in the "new era": the Nagoya University experience. *J Hepatobiliary Pancreat Sci* 2010; **17**: 449-454 [PMID: 19806294 DOI: 10.1007/s00534-009-0209-0]

42 **Lee SG**, Song GW, Hwang S, Ha TY, Moon DB, Jung DH, Kim KH, Ahn CS, Kim MH, Lee SK, Sung KB, Ko GY. Surgical treatment of hilar cholangiocarcinoma in the new era: the Asan experience. *J Hepatobiliary Pancreat Sci* 2010; **17**: 476-489 [PMID: 19851704 DOI: 10.1007/s00534-009-0204-5]

43 **Shimizu H**, Kimura F, Yoshidome H, Ohtsuka M, Kato A, Yoshitomi H, Furukawa K, Miyazaki M. Aggressive surgical resection for hilar cholangiocarcinoma of the left-side predominance: radicality and safety of left-sided hepatectomy. *Ann Surg* 2010; **251**: 281-286 [PMID: 20054275 DOI: 10.1097/SLA.0b013e3181be0085]

44 **Unno M**, Katayose Y, Rikiyama T, Yoshida H, Yamamoto K, Morikawa T, Hayashi H, Motoi F, Egawa S. Major hepatectomy for perihilar cholangiocarcinoma. *J Hepatobiliary Pancreat Sci* 2010; **17**: 463-469 [PMID: 19941010 DOI: 10.1007/s00534-009-0206-3]

45 **Regimbeau JM**, Fuks D, Le Treut YP, Bachellier P, Belghiti J, Boudjema K, Baulieux J, Pruvot FR, Cherqui D, Farges O.

Surgery for hilar cholangiocarcinoma: a multi-institutional update on practice and outcome by the AFC-HC study group. *J Gastrointest Surg* 2011; **15**: 480-488 [PMID: 21249527 DOI: 10.1007/s11605-011-1414-0]

46 **Ribero D**, Amisano M, Lo Tesoriere R, Rosso S, Ferrero A, Capussotti L. Additional resection of an intraoperative margin-positive proximal bile duct improves survival in patients with hilar cholangiocarcinoma. *Ann Surg* 2011; **254**: 776-781; discussion 781-783 [PMID: 22042470 DOI: 10.1097/SLA.0b013e3182368f85]

47 **Saxena A**, Chua TC, Chu FC, Morris DL. Improved outcomes after aggressive surgical resection of hilar cholangiocarcinoma: a critical analysis of recurrence and survival. *Am J Surg* 2011; **202**: 310-320 [PMID: 21871986 DOI: 10.1016/j.amjsurg.2010.08.041]

48 **Young AL**, Igami T, Senda Y, Adair R, Farid S, Toogood GJ, Prasad KR, Lodge JP. Evolution of the surgical management of perihilar cholangiocarcinoma in a Western centre demonstrates improved survival with endoscopic biliary drainage and reduced use of blood transfusion. *HPB* (Oxford) 2011; **13**: 483-493 [PMID: 21689232 DOI: 10.1111/j.1477-2574.2011.00328.x]

49 **Cheng QB**, Yi B, Wang JH, Jiang XQ, Luo XJ, Liu C, Ran RZ, Yan PN, Zhang BH. Resection with total caudate lobectomy confers survival benefit in hilar cholangiocarcinoma of Bismuth type III and IV. *Eur J Surg Oncol* 2012; **38**: 1197-1203 [PMID: 22992326 DOI: 10.1016/j.ejso.2012.08.009]

50 **de Jong MC**, Marques H, Clary BM, Bauer TW, Marsh JW, Ribero D, Majno P, Hatzaras I, Walters DM, Barbas AS, Mega R, Schulick RD, Choti MA, Geller DA, Barroso E, Mentha G, Capussotti L, Pawlik TM. The impact of portal vein resection on outcomes for hilar cholangiocarcinoma: a multi-institutional analysis of 305 cases. *Cancer* 2012; **118**: 4737-4747 [PMID: 22415526 DOI: 10.1002/cncr.27492]

51 **Nagino M**, Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, Nimura Y. Evolution of surgical treatment for perihilar cholangiocarcinoma: a single-center 34-year review of 574 consecutive resections. *Ann Surg* 2013; **258**: 129-140 [PMID: 23059502 DOI: 10.1097/SLA.0b013e3182708b57]

52 **Iacono C**, Ruzzenente A, Campagnaro T, Bortolasi L, Valdegamberi A, Guglielmi A. Role of preoperative biliary drainage in jaundiced patients who are candidates for pancreatoduodenectomy or hepatic resection: highlights and drawbacks. *Ann Surg* 2013; **257**: 191-204 [PMID: 23013805 DOI: 10.1097/SLA.0b013e31826f4b0e]

53 **Guiu B**, Bize P, Demartines N, Lesurtel M, Denys A. Simultaneous biliary drainage and portal vein embolization before extended hepatectomy for hilar cholangiocarcinoma: preliminary experience. *Cardiovasc Intervent Radiol* 2014; **37**: 698-704 [PMID: 23842686 DOI: 10.1007/s00270-013-0699-7]

54 **Hatfield AR**, Tobias R, Terblanche J, Girdwood AH, Fataar S, Harries-Jones R, Kernoff L, Marks IN. Preoperative external biliary drainage in obstructive jaundice. A prospective controlled clinical trial. *Lancet* 1982; **2**: 896-899 [PMID: 6126752]

55 **McPherson GA**, Benjamin IS, Hodgson HJ, Bowley NB, Allison DJ, Blumgart LH. Pre-operative percutaneous transhepatic biliary drainage: the results of a controlled trial. *Br J Surg* 1984; **71**: 371-375 [PMID: 6372935]

56 **Pitt HA**, Gomes AS, Lois JF, Mann LL, Deutsch LS, Longmire WP. Does preoperative percutaneous biliary drainage reduce operative risk or increase hospital cost? *Ann Surg* 1985; **201**: 545-553 [PMID: 2986562]

57 **Kawashima H**, Itoh A, Ohno E, Itoh Y, Ebata T, Nagino M, Goto H, Hirooka Y. Preoperative endoscopic nasobiliary drainage in 164 consecutive patients with suspected perihilar cholangiocarcinoma: a retrospective study of efficacy and risk factors related to complications. *Ann Surg* 2013; **257**: 121-127 [PMID: 22895398 DOI: 10.1097/SLA.0b013e318262b2e9]

58 **Abdalla EK**, Hicks ME, Vauthey JN. Portal vein embolization: rationale, technique and future prospects. *Br J Surg* 2001; **88**: 165-175 [PMID: 11167863 DOI: 10.1046/j.1365-2168.2001.01658.x]

59 **Capussotti L**, Vigano L, Ferrero A, Muratore A. Local surgical resection of hilar cholangiocarcinoma: is there still a place? *HPB* (Oxford) 2008; **10**: 174-178 [PMID: 18773049 DOI: 10.1080/13651820801992534]

60 **Otto G**, Romaneehsen B, Hoppe-Lotichius M, Bittinger F. Hilar cholangiocarcinoma: resectability and radicality after routine diagnostic imaging. *J Hepatobiliary Pancreat Surg* 2004; **11**: 310-318 [PMID: 15549429 DOI: 10.1007/s00534-004-0912-9]

61 **Nimura Y**, Hayakawa N, Kamiya J, Kondo S, Shionoya S. Hepatic segmentectomy with caudate lobe resection for bile duct carcinoma of the hepatic hilus. *World J Surg* 1990; **14**: 535-443; discussion 544 [PMID: 2166381]

62 **Ogura Y**, Mizumoto R, Tabata M, Matsuda S, Kusuda T. Surgical treatment of carcinoma of the hepatic duct confluence: analysis of 55 resected carcinomas. *World J Surg* 1993; **17**: 85-92; discussion 92-93 [PMID: 8447147]

63 **Sugiura Y**, Nakamura S, Iida S, Hosoda Y, Ikeuchi S, Mori S, Sugioka A, Tsuzuki T. Extensive resection of the bile ducts combined with liver resection for cancer of the main hepatic duct junction: a cooperative study of the Keio Bile Duct Cancer Study Group. *Surgery* 1994; **115**: 445-451 [PMID: 8165536]

64 **Kow AW**, Wook CD, Song SC, Kim WS, Kim MJ, Park HJ, Heo JS, Choi SH. Role of caudate lobectomy in type III A and III B hilar cholangiocarcinoma: a 15-year experience in a tertiary institution. *World J Surg* 2012; **36**: 1112-1121 [PMID: 22374541 DOI: 10.1007/s00268-012-1497-0]

65 **Nagino M**. Perihilar cholangiocarcinoma: a surgeon's viewpoint on current topics. *J Gastroenterol* 2012; **47**: 1165-1176 [PMID: 22847554 DOI: 10.1007/s00535-012-0628-6]

66 **Ebata T**, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, Nimura Y, Nagino M. Hepatopancreatoduodenectomy for cholangiocarcinoma: a single-center review of 85 consecutive patients. *Ann Surg* 2012; **256**: 297-305 [PMID: 22750757 DOI: 10.1097/SLA.0b013e31826029ca]

67 **Kitagawa Y**, Nagino M, Kamiya J, Uesaka K, Sano T, Yamamoto H, Hayakawa N, Nimura Y. Lymph node metastasis from hilar cholangiocarcinoma: audit of 110 patients who underwent regional and paraaortic node dissection. *Ann Surg* 2001; **233**: 385-392 [PMID: 11224627]

68 **Nagino M**. Cutting edge of an aggressive surgical approach for perihilar cholangiocarcinoma. *Updates Surg* 2013; **65**: 81-83 [PMID: 23460256 DOI: 10.1007/s13304-013-0204-5]

69 **Neuhaus P**, Thelen A, Jonas S, Puhl G, Denecke T, Veltzke-Schlieker W, Seehofer D. Oncological superiority of hilar en bloc resection for the treatment of hilar cholangiocarcinoma. *Ann Surg Oncol* 2012; **19**: 1602-1608 [PMID: 21964888 DOI: 10.1245/s10434-011-2077-5]

70 **Miyazaki M**, Kato A, Ito H, Kimura F, Shimizu H, Ohtsuka M, Yoshidome H, Yoshitomi H, Furukawa K, Nozawa S. Combined vascular resection in operative resection for hilar cholangiocarcinoma: does it work or not? *Surgery* 2007; **141**: 581-588 [PMID: 17462457 DOI: 10.1016/j.surg.2006.09.016]

71 **Nagino M**, Nimura Y, Nishio H, Ebata T, Igami T, Matsushita M, Nishikimi N, Kamei Y. Hepatectomy with simultaneous resection of the portal vein and hepatic artery for advanced perihilar cholangiocarcinoma: an audit of 50 consecutive cases. *Ann Surg* 2010; **252**: 115-123 [PMID: 20531001 DOI: 10.1097/SLA.0b013e3181e463a7]

72 **Chen YL**, Chen WB, Wan YY, Li WG, Huang ZQ, Wu XT, Yang J, Yang L. Effects of partial portal vein arterialization on liver regeneration after hepatectomy in minipigs with obstructive jaundice. *Chin Med J* (Engl) 2012; **125**: 2302-2305 [PMID: 22882852]

73 **Sano T**, Shimada K, Sakamoto Y, Yamamoto J, Yamasaki S, Kosuge T. One hundred two consecutive hepatobiliary resections for perihilar cholangiocarcinoma with zero mor-

tality. *Ann Surg* 2006; **244**: 240-247 [PMID: 16858186 DOI: 10.1097/01.sla.0000217605.66519.38]
74 **Schiffman SC**, Reuter NP, McMasters KM, Scoggins CR, Martin RC. Overall survival peri-hilar cholangiocarcinoma: R1 resection with curative intent compared to primary endoscopic therapy. *J Surg Oncol* 2012; **105**: 91-96 [PMID: 21815152 DOI: 10.1002/jso.22054]
75 **Hasegawa S**, Ikai I, Fujii H, Hatano E, Shimahara Y. Surgical resection of hilar cholangiocarcinoma: analysis of survival and postoperative complications. *World J Surg* 2007; **31**: 1256-1263 [PMID: 17453285 DOI: 10.1007/s00268-007-9001-y]
76 **Cannon RM**, Brock G, Buell JF. Surgical resection for hilar cholangiocarcinoma: experience improves resectability. *HPB* (Oxford) 2012; **14**: 142-149 [PMID: 22221577 DOI: 10.1111/j.1477-2574.2011.00419.x]
77 **Pandey D**, Lee KH, Tan KC. The role of liver transplantation for hilar cholangiocarcinoma. *Hepatobiliary Pancreat Dis Int* 2007; **6**: 248-253 [PMID: 17548246]
78 **Meyer CG**, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. *Transplantation* 2000; **69**: 1633-1637 [PMID: 10836374]
79 **Gores GJ**, Darwish Murad S, Heimbach JK, Rosen CB. Liver transplantation for perihilar cholangiocarcinoma. *Dig Dis* 2013; **31**: 126-129 [PMID: 23797134 DOI: 10.1159/000347207]
80 **Ito F**, Cho CS, Rikkers LF, Weber SM. Hilar cholangiocarcinoma: current management. *Ann Surg* 2009; **250**: 210-218 [PMID: 19638920 DOI: 10.1097/SLA.0b013e3181afe0ab]
81 **Pichlmayr R**, Weimann A, Klempnauer J, Oldhafer KJ, Maschek H, Tusch G, Ringe B. Surgical treatment in proximal bile duct cancer. A single-center experience. *Ann Surg* 1996; **224**: 628-638 [PMID: 8916878]
82 **Rosen CB**, Heimbach JK, Gores GJ. Liver transplantation for cholangiocarcinoma. *Transpl Int* 2010; **23**: 692-697 [PMID: 20497401]

P- Reviewer: Chetty R, Plentz RR **S- Editor**: Wen LL
L- Editor: Wang TQ **E- Editor:** Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com