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Current surgical treatment for bile duct cancer

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Abstract

Since extrahepatic bile duct cancer is difficult to diagnose and to cure, a safe and radical surgical strategy is needed. In this review, the modes of infiltration and spread of extrahepatic bile duct cancer and surgical strategy are discussed. Extended hemihepatectomy, with or without pancreatoduodenectomy (PD), plus extrahepatic bile duct resection and regional lymphadenectomy has recently been recognized as the standard curative treatment for hilar bile duct cancer. On the other hand, PD is the choice of treatment for middle and distal bile duct cancer. Major hepatectomy concomitant with PD (hepatopancreatoduodenectomy) has been applied to selected patients with widespread tumors. Preoperative biliary drainage (BD) followed by portal vein embolization (PVE) enables major hepatectomy in patients with hilar bile duct cancer without mortality. BD should be performed considering the surgical procedure, especially, in patients with separated intrahepatic bile ducts caused by hilar bile duct cancer. Right or left trisectoriectomy are indicated according to the tumor spread and biliary anatomy. As a result, extended radical resection offers a chance for cure of hilar bile duct cancer with improved resectability, curability, and a 5-year survival rate of 40%. A 5-year survival rate has ranged from 24% to 39% after PD for middle and distal bile duct cancer.

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Key words: Extrahepatic bile duct cancer; Cholangiocarcinoma; Biliary drainage; Portal vein embolization; Extended hemihepatectomy; Pancreatoduodenectomy; Hepatopancreatoduodenectomy; Right trisectionectomy; Left trisectoriectomy

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INTRODUCTION

Extrahepatic bile duct cancer is difficult to diagnose in the early stage. Most patients with bile duct cancer have developed jaundice at presentation, and the tumor stage is already advanced. The anatomical relationships between hepatic hilar structures and modes of tumor extension are complicated, and this has resulted in low resectability and curability, high morbidity and mortality, and poor long-term survival rate[1-9]. Because of the advances of clinical imaging, such as magnetic resonance cholangiography (MRC) and helical computed tomography (CT)[10,11], the results of bile duct cancer diagnosis have improved, and the number of candidates for surgical resection has increased.

Radical resection is still the only a chance for cure, and various types of surgical procedure have been applied[1-3,6,12-14]. Extended hemihepatectomy has recently been recognized as the standard curative treatment for hilar bile duct cancer and has acceptable mortality[15-19]. Pancreatoduodenectomy (PD), on the other hand, is the choice of treatment for middle and distal bile duct cancer[20-24], and major hepatectomy concomitant with PD (HPD) has been applied to selected patients with widespread tumors[17,18,25-27]. However, these extensive radical procedures are not always safe, because there are risks of postoperative liver failure and pancreatic leakage. Radical resection with a safe and beneficial strategy is needed in the treatment of bile duct cancer. Proper choice of surgical procedure according to the modes and patterns of tumor infiltration is important for curative resection. Preoperative treatments, including biliary drainage (BD) and portal vein embolization (PVE), are necessary before major hepatectomy. In this article we review the current treatment of extrahepatic bile duct cancer and elucidate safe and beneficial surgical treatments and the surgeon's role in treatment.

CLASSIFICATION OF BILE DUCT CANCER

Cholangiocarcinoma is defined as any tumor arising from the ductal epithelium of the biliary tree and is classified as intrahepatic or extrahepatic according to its location[28,29]. Intrahepatic cholangiocarcinoma is usually treated as a hepatic tumor, because it requires hepatic resection alone.
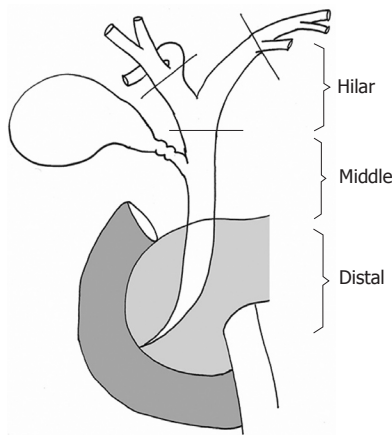
Figure 1 Schema of extrahepatic bile duct.
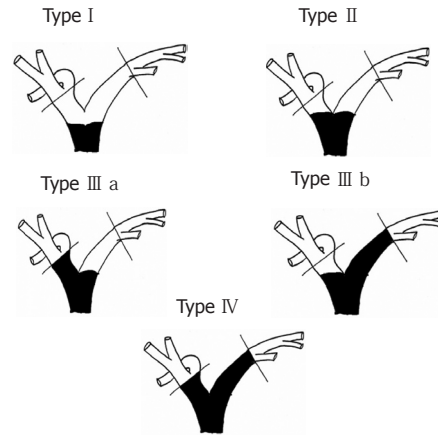
Figure 2 Bismuth-Corlette classification of hilar bile duct cancer[9].

In this article we have focused on the surgical treatment of extrahepatic bile duct cancer, which is classified according to the primary site into hilar, middle, and distal bile duct cancer[30] (Figure 1). The longitudinal extent of bile duct cancers that involve the bifurcation of the hepatic duct is classified according to a modified Bismuth-Corlette classification[2,9] (Figure 2).

MODE OF INFILTRATION AND SPREAD OF BILE DUCT CANCER

Longitudinal tumor spread along the biliary tree

Infiltration by bile duct cancer includes both longitudinal extension and vertical invasion. Microscopic extension of bile duct cancer beyond the border visualized by cholangiography or the margin observed macroscopically is often detected, and is diagnosed as a microscopically positive margin (R1). Longitudinal extension consists of superficial and submucosal infiltration and includes sometimes direct, lymphatic, or perineural invasion[31-36]. Sakamoto *et al*[35] pointed out a correlation between the gross type of the tumor and the pattern of infiltration beyond the macroscopic margin at the proximal border. The submucosal spread was predominant in infiltrating type, and the mean length was 6 mm. The superficial extension was predominant in papillary and nodular types, and the mean length was 20 mm. Ebata *et al*[36] investigated 80 resected specimens with microscopically positive margin and observed invasive (submucosal) extent within 10 mm in all the cases, and non-invasive (superficial) spread within 20 mm in 90% of the cases. Considering these reports, a macroscopic surgical margin over 10 mm is preferable in the invasive type and over 20 mm in the papillary and nodular types. Intraoperative pathologic examination of frozen sections is also advocated to confirm the margin of the cut end of the bile duct. When the margin is positive for cancer, additional resection is necessary to obtain R0 resection whenever possible.

Vertical invasion of the bile duct

Hilar bile duct cancer vertically infiltrates into the hepatoduodenal ligament, in which the hepatic artery and the portal vein are located adjacent to the bile duct. Skeltonization of vessels in the hepatoduodenal ligament

and clearance of all perivascular connective tissue is standard surgical procedure[15,37,38]. Hilar bile duct cancer easily invades the right hepatic artery, which usually lies behind the common bile duct, and involves the portal vein. If the tumor shows the signs of invasion of the perivascular connective tissue, en bloc resection of the right hepatic artery is advocated to obtain a negative surgical margin; therefore, right hemihepatectomy is recommended. If tumor invasion of the portal vein is suspected based on the preoperative imaging or the intraoperative findings, combined resection of the portal vein and reconstruction are the treatment of choice to obtain a negative radical margin[39-41].

Need for hepatectomy and caudate lobectomy

When the hilar bile duct cancer has infiltrated the hepatic duct confluence, 3-dimensional knowledge of the hepatic hilum is required to determine the extent of the tumor because of the complicated anatomical relationships. Hilar bile duct cancer spreads not only to the right and left bile ducts but in a craniad and dorsal direction along the thin bile ducts. There are two key points to achieving radical resection of hilar bile duct carcinoma. The first is removal of the liver parenchyma adjacent to the hepatic hilum together with the hilar plate, and extended right or left hepatectomy is preferable for this purpose to remove the infiltration of cancer to the right and left bile ducts. The second key point is caudate lobectomy and resection of the inferior area of segment IV to extirpate cancer infiltration to the thinner bile ducts near the hilum.

The necessity of resecting the caudate lobe has been described by Japanese authors[12,13,42-44]. Nimura *et al*[43] firstly described caudate lobectomy for hilar bile duct cancer. The clinical efficacy of caudate lobe resection was first described by Sugiura *et al*[13]. The 5-year survival rate in their retrospective study was 46% with caudate lobectomy and 12% without caudate lobectomy.

Cholangiography of a resected specimen obtained by extended left hemihepatectomy with caudate resection showed that the caudate branches of the bile originated from the confluence of the hepatic ducts and that hilar bile duct cancer invaded these branches (Figure 3).

DIAGNOSIS

Resectability was assessed and the type of surgical treatment was selected according to the location and extent of the tumor as determined by ultrasonography, helical-CT, direct cholangiography, and MRCP[10]. Patients with para-aortic lymph node metastasis or other distant metastases were not included as candidates for resectional surgery. Direct cholangiography *via* the percutaneous or endoscopic route provides useful findings, but cholangitis may occur after repeated cholangiography in patients whose right and left hepatic ducts are separated by hilar bile duct cancer because the bile is contaminated with bacteria three days after biliary drainage and undrained bile ducts are infected as a result of reflux of the contaminated bile. Direct cholangiography should be restricted to the time of the first puncture and the evening of the day before surgery if the bile ducts are separated[18]. MRCP provides information regarding the entire biliary tree and eliminates the need for direct cholangiography of the whole biliary tree.

Helical contrast CT angiography as well as conventional angiography reveals not only tumor invasion of the vessels in the hepatoduodenal ligament but also vascular anomalies, especially of the hepatic arteries, which are sometimes a determinant of the operative procedure. Aberrant right hepatic arteries originating from the root of the superior mesenteric artery and aberrant left hepatic arteries originating from the left gastric artery are invaded late by bile duct cancer. Preserving the aberrant arteries increases the probability of curative resection by extended right or left hemihepatectomy.

It is sometimes difficult to make a definite diagnosis of bile duct cancer. Bile cytology or brushing biopsy is the choice of diagnosis, but benign lesions such as primary sclerosing cholangitis, cannot be denied in the treatment of bile duct cancer. The incidence of benign lesion in patients with hilar obstruction ranges from 8% to 15%[45,46]. Surgeons should consider the possibility of benign lesions when treating bile duct cancer. Radical surgery of a lesion suspected of being a malignant neoplasm is justified under the condition of low mortality rate even at the risk of benign diseases.

PREOPERATIVE TREATMENT

Biliary drainage

The aim of preoperative BD is to improve liver function and reduce morbidity and mortality after radical surgery with major hepatectomy, i.e. resection of more than three segment of the liver[47-51]. However, instead of elucidating the benefits of preoperative BD previous reports have emphasized the adverse effects of BD, i.e. infectious complications due to bile contamination and tract seeding[47-58]. Sewnath et al[56] reviewed and summarized randomized controlled and comparative cohort studies, comparing surgery plus preoperative BD with surgery without preoperative BD, and they performed a meta-analysis of the efficacy of preoperative BD. The results however, failed to show an effect of preoperative BD on the surgery. However, the following problems determine
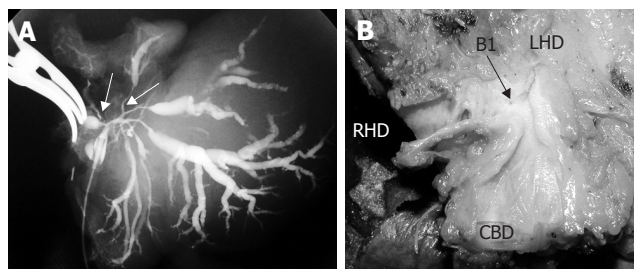

Figure 3 Tumor infiltration of the roots of the caudate branches; **A**: Cholangiography of a resected specimen. Hilar bile duct cancer has infiltrated the root of the caudate branches (B1) arising from the confluence of the hepatic duct (arrows); **B**: Gross appearance of the resected tumor. The caudate branch opens into the hilar neoplasm.

the pros and cons of preoperative BD based on the previous reports[18,59]. First, the rate of radical resection or major hepatectomy was too low to examine the effect of BD on surgery in those studies. The rate of resection in randomized controlled studies is only 15% on average and the other procedures were palliative treatments. The average resectability rate was 90% in the comparative cohort studies, but pancreatoduodenectomy composed nearly 90% of resected cases and hemihepatectomy only 2%. To perform major hepatectomy in patients with jaundice for hilar bile duct cancer is most likely to develop postoperative liver failure. Second, in the previous studies, recovery of hepatic function was insufficient, since BD was only performed for 10-14 d and the surgical interventions were carried out at a total bilirubin value of about 10 mg/dL[48,50]. By contrast, the studies from Japan insisted that radical surgery be performed after complete recovery from jaundice, i.e., a total bilirubin decrease to under 2.0 mg/dL[15,16,18]. It takes 4-6 wk for liver function to recover after BD for jaundice[47,60,61]. Finally, most tube-related trouble is due to poor technical skill, such as drainage tube failure and cholangitis caused by unnecessary cholangiography. Slipping of the drainage tube out of the bile duct can be prevented by careful management of the BD tube and by using balloon catheters or pig-tail catheters.

Since suppurative cholangitis is not a rare complication after BD, many reports have pointed out that bile contamination increases postoperative infectious complications and mortality, and that preoperative BD should be avoided. Cholangitis is caused by pushing the contaminated bile into the undrained area during cholangiography or by occlusion of the drainage tube. The most important means of preventing cholangitis is not to perform cholangiography after PTBD in patients whose right and left bile ducts are separated by tumor infiltration. Cholangiography should be limited to the time of PTBD and the afternoon of the day before the operation, because bile juice becomes contaminated by bacteria within 3 d after PTBD.

Once cholangitis has developed regardless of the cause, the treatment of choice is BD by either the percutaneous transhepatic or endoscopic retrograde route. Criticism of preoperative BD due to the risk of cholangitis is nonsense, because doctors claim such opinion indicate that they cannot treat the patients who have cholangitis not by
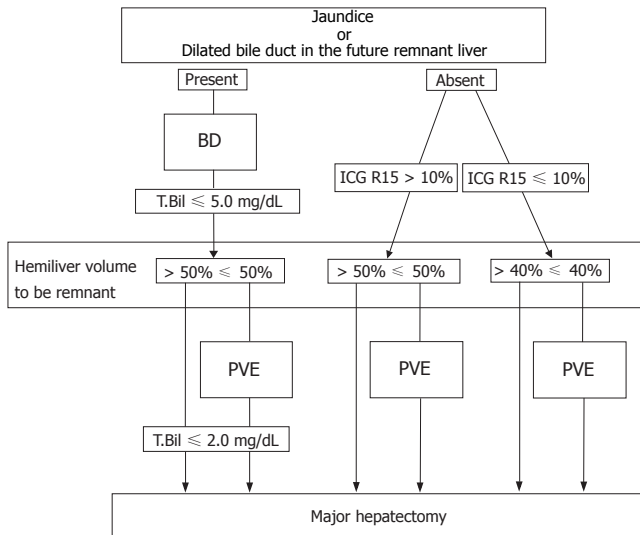
Figure 4 Flowchart of preoperative treatment. If a patient had jaundice or there were dilated bile ducts in the future remnant liver, biliary drainage (BD) was performed. Surgical interventions were scheduled after sufficient recovery of hepatic function. Portal vein embolization (PVE) was carried out to avoid postoperative liver failure, depending on the liver function and the liver volume to be resected.

BD. Bile from the BD tube should be cultured, and the sensitivity of isolates to antibiotics should be checked routinely. During the operation, a solution of antibiotic to which the culture are sensitive should be scattered into the abdominal cavity before closing the wound.

The route of BD is either percutaneous transhepatic or endoscopic retrograde. The only drawback of the percutaneous transhepatic route is catheter tract seeding (described below in detail). The endoscopic route, on the other hand, is closely associated with retrograde infection, and thus it is not advocated for hilar obstruction. The biliary stent tube should be replaced every two weeks to avoid tube occlusion by debris in patients in whom an endoscopic retrograde BD (ERBD) tube has been inserted[62].

Points of preoperative BD procedure are listed below. The following should be taken into consideration: (1) Externally drained bile juice should be taken orally[63], (2) Radical operation should be performed after sufficient recovery of liver function[15,16,18], (3) BD should be performed if hepatectomy is scheduled[64], (4) ERBD stent tube should be replaced every two weeks, (5) Bile culture should be performed routinely, and isolates should be tested for the antibiotic sensitivity[58].

For hilar obstruction with interruption of communication between the right and the left hepatic duct, the following should be taken into consideration (1) PTBD of the future remnant liver alone is the first choice[17,18,65,66], (2) The endoscopic route is not advocated[53,57,67,68], (3) To avoid cholangitis, preoperative cholangiography should be performed only when the tube is inserted and on the evening before the operation[18].

Catheter tract seeding is a problem related to PTBD, and its incidence has been reported to be 5%-10%[18,69]. Multiple BD and PTCS may increase the risk of seeding, but the risk can be decreased by the draining only the future remnant liver and using the minimum number of BD tubes. Tract seeding did not affect outcome because

the primary tumors were already far-advanced and most patients had multiple recurrences. Sakata et al[69] reported that resection of an isolated metastasis along the catheter tract may prolong survival. Catheter tract seeding is not a rare complication in the treatment of the malignant biliary obstruction, but its incidence is acceptable.

Portal vein embolization

In 1982, Makuuchi et al[70,71] were the first to apply PVE to prevent liver failure after extended hemihepatectomy in patients with hilar cholangiocarcinoma. Major hepatectomy results in massive reduction of the liver volume and a increase in portal pressure. If PVE is performed preoperatively, the portal hypertension can be tolerated, and the rate of liver volume loss decreases due to the atrophy-hypertrophy complex theory. Kubota et al[72] showed indication criteria of PVE according to the volume of liver to be resected, which was calculated from CT, and ICG R15 value. Several recent reports have confirmed the safety of major hepatectomy following PVE for patients with hilar bile duct cancer and obstructive jaundice[16-18,38,73]. The rate of liver volume to be preserved increased by 8%-12% two weeks after PVE[18,74,75]. In Western countries, evaluations of liver volume after PVE have been made after 4-6 wk. The wait between PVE and operation is shorter in the reports from Japan, but was adequate to perform hepatic resection safely.

Safe strategy for major hepatectomy in patients with hilar bile duct cancer

Seyama et al[18] described the safe strategy for hilar bile duct cancer that includes BD and PVE. A flow chart for preoperative treatment is shown in Figure 4. If a patient showed evidence of jaundice or there were dilated bile ducts in the future remnant liver, BD was performed, in principle only in the future remnant liver. Whether PVE was indicated depended on liver function and the volume of the future remnant liver, which was calculated by CT volumetry. In patients with normal liver function, i.e. an ICG R15 value under 10%, PVE was indicated when the remnant hemiliver volume was less than 40%. In patients with jaundice or with an ICG R15 value over 10%, PVE was indicated if the remnant hemiliver volume was less than 50%. Since the standard operative procedure for hilar bile duct cancer is an extended hemihepatectomy, including the whole S1, the remaining hemiliver volume should have a margin from the safety zone. After re-evaluation of the liver volume to be resected, hepatectomy was performed if the patient fulfilled the criteria. Figure 5 showed the intraoperative findings after BD of the future remnant liver followed by PVE of the right portal vein. The right liver was markedly atrophic, and the BD tube was inserted into the bile duct in segment 3, which drained only the future remnant left liver. In this patient, extended right hemihepatectomy was carried out.

SURGICAL TREATMENT FOR BILE DUCT CANCER

In view of their modes and patterns of infiltration, the best treatment for hilar bile duct cancer is extrahepatic bile duct

Figure 5 Intraoperative view at laparotomy after biliary drainage and portal vein embolization. A percutaneous transhepatic biliary drainage tube (arrow) has been inserted into the bile duct of segment 3. The right liver is markedly atrophic, and there is a clear line of demarcation between the right and left liver.

Figure 6 Indications for left trisectoriectomy according to tumor location and the bile duct variations in the anatomy of the right lateral branch of the bile duct. Double lines indicate the scheduled cut end of the bile duct. Type A, ordinary bifurcation; extended right hepatectomy is the choice of treatment. Type B, the right lateral branch originates from the common hepatic duct; left trisectoriectomy, preserving the right lateral branch, is a useful alternative in Types B1 and B2. Type C, the right lateral branch originates from the left hepatic duct; left trisectoriectomy may provide a longer bile duct margin.
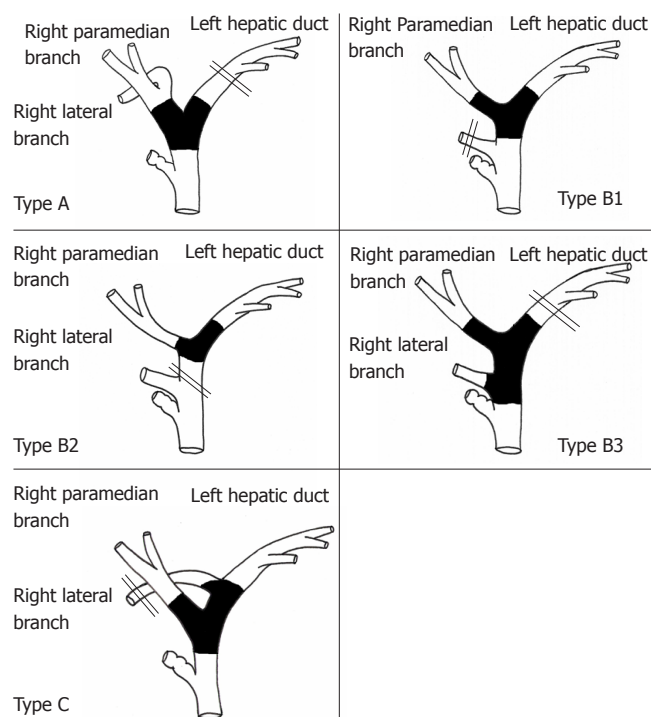
resection plus hepatectomy and regional lymphadenectomy, and the best treatment for middle and distal bile duct cancer is pancreatoduodenectomy. Lymph node dissection includes the nodes within the hepatoduodenal ligament, behind the pancreatic head, and along the common hepatic artery. Some authors have reported extended lymphadenectomy including para-aortic lymph nodes, but the incidence of para-aortic lymph node metastasis by bile duct cancer is lower than by pancreatic cancer. Since there is no evidence of a survival benefit[76,77], extended lymph node dissection is not justified.

Extended hemihepatectomy for hilar bile duct carcinoma

Because of its radicality and simplicity, extended hemihepatectomy is recognized as the standard surgical procedure for hilar bile duct cancer[15,17,18,27,38,73]. Extended right hemihepatectomy consists of resection of the right liver, the inferior part of Couinaud's segment IV, and the entire caudate lobe. Extended left hemihepatectomy consists of resection of the left liver, the hilar part of the anterior segment, and most of the caudate lobe. Even in patients with Bismuth type I or type II, extended hemihepatectomy is needed to achieve curative resection according to the mode of tumor extension[17,18,73]. If the tumor is predominantly on the right side or centrally located, extended right hepatectomy is selected. Kawasaki *et al*[17] explained why right hepatectomy is more likely to be associated with a negative margin than left hepatectomy based on the anatomic considerations, i.e. length of the extrahepatic part of each hepatic duct, location of the common hepatic duct in the hepatoduodenal ligament, facility for systematic caudate lobectomy, and ease of portal vein reconstruction. Extended left hemihepatectomy is indicated for left-side-dominant tumor. If the tumor has spread diffusely into the intrapancreatic bile duct, pancreatoduodenectomy is performed simultaneously[27] (HPD, described later).

Right or left trisectoriectomy for hilar bile duct carcinoma

Right or left trisectoriectomy is one of the most extensive resections because of the massive loss of volume of the hepatic parenchyma[78-80]. Hilar bile duct cancer widely invades the hepatic hilum (Bismuth type IV), resulting in jaundice, and sometimes requires trisectoriectomy for curative resection. Right or left trisectoriectomy is advantageous in terms of obtaining a cancer-free margin in the hepatic ducts. A negative hepatic margin was obtained in 75% of cases treated by left trisectoriectomy and 87.5% of cases treated by right trisectoriectomy, both rates are higher than obtained by extended hemihepatectomy[79,80]. Variation in the anatomy of the right lateral branch should be taken into consideration to obtain adequate surgical margin (Figure 6). Type A is an ordinary bifurcation, and extended right hepatectomy is the choice of treatment. If the right lateral branch originates directly from the common hepatic duct (Figure 6 Type B1-2), left trisectoriectomy, which preserves the right lateral branch, is a useful alternative. When the right lateral branch originates from the left hepatic duct, left trisectoriectomy may provide a longer bile duct margin than other hepatic resection (Figure 6 Type C). Since the aberrant right hepatic artery originates from the SMA, which runs behind the portal vein and the right-dorsal aspect of the hepatoduodenal ligament, is hardly invaded by bile duct cancer; left trisectoriectomy, which preserves the right lateral branch of the right hepatic artery, is a useful alternative for advanced hilar cholangiocarcinoma. However, the operative risk of trisectoriectomy is greater than that of extended hemihepatectomy, and preoperative BD of the future remnant liver and PVE are indispensable. Nagino *et al*[80] reported a mortality rate of 7.1% after right
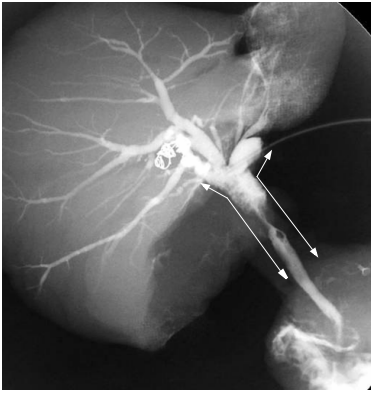
Figure 7 Cholangiography of the resected specimen by HPD. The tumor is located in the common hepatic duct (Bismuth-Corllete type 2), and microscopic examination showed superficial spread to the right and left hepatic duct and the intrapancreatic part of the common bile duct (arrows).

trisectoriectomy despite preoperative PVE. Shimada et al[79] reported 12 consecutive cases of left trisectoriectomy for hilar cholangiocarcinoma with no mortality after BD followed by PVE. Proper patient selection and adequate preoperative treatment are required when radical high-risk operations, such as trisectoriectomy, are preformed for hilar bile duct cancer.

Limited resections for hilar bile duct cancer

Parenchyma preserving hepatectomy is a less invasive procedure for hilar bile duct cancer than major hepatectomy. The drawback of the procedure is high incidence of positive margins because of tumor spread along the bile duct, although various type of hepatic resection have been used; segmental, S4 + S1, S4a + S5 + S1, S1, and extended hilar resection[14,81,82]. Other problems include the complexity of the surgical procedure, which takes a great deal of time, intraoperative bleeding, and the difficulty of biliary reconstruction. Consequently, parenchyma preserving hepatectomy for hilar bile duct cancer is the useful alternative in patients in poor general condition or with high-risk factors.

Bile duct resection without hepatectomy is the most minimally invasive, least radical surgical treatment. It is indicated only when the primary tumor is located in the middle of the common hepatic duct and there is no invasion or spread. It is also an option for high-risk patients.

Surgery for middle and distal bile duct cancer

Pancreatoduodenectomy is the treatment of choice for middle and lower bile duct cancer. The pylorus preserving Whipple procedure (PpPD) is commonly performed, and the short- and long-term results of PpPD are comparable to those of standard PD[83-85]. When a middle bile duct cancer arises midway along the extrahepatic duct, the decision has to be made as to whether PD or extended hemihepatectomy is more appropriate according to the tumor location and extension.

Indications for hepatopancreatoduodenectomy

Hepatopancreatoduodenectomy (HPD) has been used to treat biliary malignancies and is a useful alternative for the treatment of bile duct cancer. The clinical indications are longitudinal tumor spread from the hepatic duct to the intrapancreatic bile duct or massive lymph node metastases along the bile duct and behind the pancreatic head. Massive lymph node metastases are not a good indication because the presence of lymph node metastases is itself a negative prognostic factor. However, postoperative hospital mortality has been very high. Nimura et al[26] firstly presented a considerable number of patients who had undergone HPD, hospital mortality was as high as 35% and 5-year survival was only 6%. The causes of postoperative mortality after HPD are postoperative liver failure and leakage of pancreatojejunostomy resulting in bleeding from the major arteries. BD followed by PVE is indispensable to prevent postoperative liver failure[17,18,27]. A two-stage operation, in which reconstruction of the pancreatic duct is the second step, has been reported to reduce the risk of leakage of the pancreatic juice[86-88]. Miyagawa et al[27] firstly reported twelve consecutive cases of HPD without mortality, applying BD followed by PVE and staged reconstruction of the pancreatic duct.

Figure 7 is a cholangiography of a resected specimen obtained by HPD. The common hepatic duct was obstructed (Bismuth type 2), and the tumor had superficially spread to the right and left hepatic duct and the intrapancreatic part of the common bile duct. This case was considered to be a good candidate for HPD, and all the margins were negative in spite of the wide tumor spread. Pathological examination revealed that the depth of invasion was to the subserosa and that there were five lymph node metastases, all close to the bile duct. The postoperative course after HPD was uneventful, and there was no liver failure. The patient is alive without tumor recurrence as of 10 mo after surgery.

Combined vascular resection and reconstruction

The value of portal vein resection and reconstruction in the treatment of bile duct cancer is still controversial. Previously, invasion of a major vessel meant an unresectable tumor. Recent reports have shown improved results when portal vein resection and reconstruction are performed together with major hepatectomy[39-41,89]. Neuhaus et al[66] reported a 5-year survival rate of 65% after curative resection of hilar bile duct cancer with portal vein resection and reconstruction. Although their case series excluded the 60-d deaths (mortality rate of 17%) and non-curative resections, the results indicated that portal vein reconstruction concomitant with hepatectomy improves the probability of long-term survival. Interestingly, macroscopic portal vein invasion was a significant prognostic factor, but microscopic invasion was not[40,66]. When there is severe adhesion between the tumor and portal vein, combined resection and reconstruction is needed to obtain a negative surgical margin. Kondo et al[89] advocated portal vein resection and reconstruction prior to hepatic dissection during extended right hepatectomy, and the procedure enables no-touch resection. On the other hand, portal vein reconstruction increases the risk of major hepatectomy. The reported mortality of portal vein reconstruction for hilar bile duct cancer is 10%-20%, but recent studies have shown that PVE improves mortality[17,18,73]. PVE is recommended to increase the safety of major hepatectomy with portal vein reconstruction.

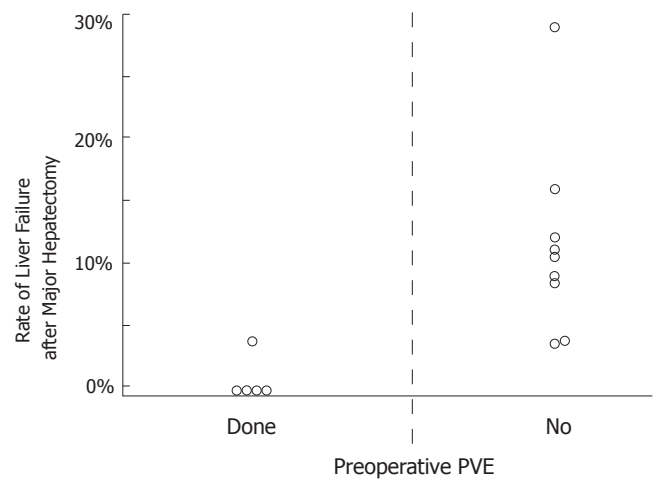**Table 1 Review of the literature on major hepatectomy for hilar bile duct carcinoma**

Author	Year	Period	Total resection	Rate of R0 (%)	Major Hx	MH/ resection (%)	BD	PVE	Liver failure (%)	Mortality	5-yr survival rate (%)
Miyagawa[16]	1995	1989-1994	37		33	89	Done	Done	0.0	0.0	NA
Pichlmayr[92]	1996	1975-1993	125	73	92	74	No	No	10.5	12.7	26.3[1]
Klempnauer[93]	1997	1971-1995	151	78	111	74	No	No	3.4	11.7	32.0[1]
Nagino[82]	1998	1977-1996	138	78	109	79	Done	Done[4]	8.0	9.7	25.8[2]
Burke[94]	1998	1991-1997	30	83	22	73	No	No	NA	6.6	45.0
Ogura[95]	1998	1976-1995	66	55	31	47	Done	No	15.9	2.2	NA
Kosuge[38]	1999	1980-1997	65	52	52	80	Done	Done[4]	10.8	9.2	34.8
Neuhaus[66]	1999	1988-1998	95	61	66	69	Done	(TAE)	NA	9.0	22.0[3]
Launois[96]	1999	1968-1993	40	80	22	55	No	No	NA (9)	12.5	12.5
Miyazaki[97]	1999	1981-1998	93	70	66	71	Done	Partially	29.0	12.0	36.0
Gerhards[98]	2000	1983-1998	112	14	32	29	Done	No	12.0	25.0	NA
Todoroki[99]	2000	1976-1998	98	14	32	33	Done	No	8.4	5.0	28.0
Jarnagin[100]	2001	1991-2000	80	78	62	78	Not routine	No	3.2	11.0	39.0
Seyama[18]	2003	1989-2001	67	64	58	87	Done	Done	0.0	0.0	40.0
Kawasaki[17]	2003	1991-2000	79	68	69	87	Done	Done	0.0	1.3	40.0
Kondo[73]	2004	1999-2002	40	95	26	65	Done	Done	0.0	0.0	40 (3-yr)
Rea[101]	2004	1979-1997	NA	80	46	NA	Done	No	11.0	9.0	26.0
Hemming[19]	2005	1997-2004	53	80	52	98	Done	Done	3.7	9.0	35.0

Hx: hepatectomy; NA: not available; R0: microscopic negative margin; BD: biliary drainage; PVE: portal vein embolization. 1, these two reports were from the same center; 2, curative Hx 97 cases; 3, total 95 cases; 4, PVE was started in the middle of the study periods.
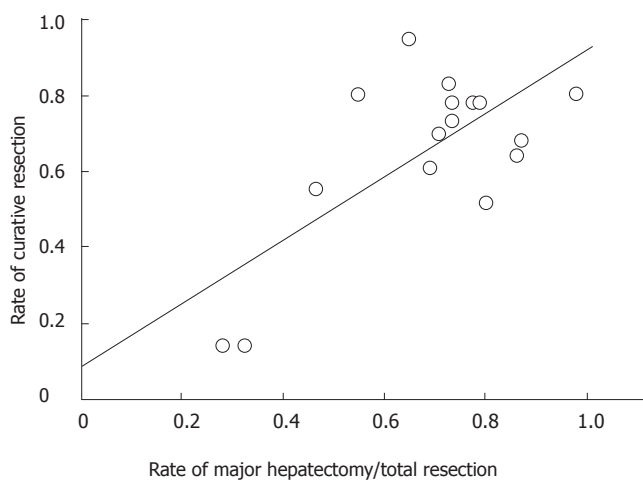
Figure 8 Graph of data from a literature review of the relationship between curative resection and major hepatectomy rate. The studies are listed shown in Table 1. Curative resection is defined as a microscopic ally negative margin. Linear approximation showed a significant correlation between the rate of major hepatectomy and curative resection (P = 0.0027, R = 0.7).

Figure 9 Graph of data from a literature review of the relationship between the preoperative portal vein embolization (PVE) and the rate of postoperative liver failure after major hepatectomy for hilar bile duct cancer. PVE significantly reduced the incidence of postoperative liver failure (P = 0.0113).

The clinical significance of combined resection and reconstruction of the hepatic artery of the remnant liver has not been resolved[17,18,39-41,90,91]. Reconstruction of the hepatic artery has been performed less frequently than reconstruction of the portal vein, because the conditions that require combined resection of the hepatic artery of the remnant liver often mean a locally far advanced tumor. Although there have been recent reports of major hepatectomy with reconstruction of the hepatic artery being performed safely with acceptable mortality rates (0-8%)[90,91], since it is more dangerous than major hepatectomy without reconstruction[41], at present reconstruction of the hepatic artery together with major hepatectomy is advocated if the tumor can be resected without residual tumor at any surgical margin.

SHORT-AND LONG-TERM OUTCOME

As mentioned above, major hepatectomy is the most suitable surgical procedure for removing hilar bile duct cancer with curative intent, and it is the standard procedure. Table 1 shows the results of major hepatectomy for hilar bile duct cancer over the last 10 years based on the review of the literature[16-19,38,66,73,82,92-101]. Hepatectomy improved the resectability and curability of the surgical resection for hilar bile duct cancer. Launois *et al*[96] reviewed selected studies and pointed out the positive correlation between the resectability rate and hepatectomy. The rate of major hepatectomy and curability are plotted in Figure 8 and show a significant positive correlation (P = 0.0027, R = 0.7). Recent reports have shown that the 5-year survival rate for hilar bile duct cancer treated by major hepatectomy has improved to 40%.

A high rate of postoperative liver failure and high mortality rate have been mentioned as the drawbacks of major hepatectomy for hilar bile duct cancer despite its radicality. Table 1 shows that BD alone does not reduce the rate of postoperative liver failure, and that major hepatectomy can be carried out without liver failure or mortality by using preoperative PVE together with BD. Rates of postoperative liver failure of 10%-20% had have been reported without PVE, and PVE has significantly reduced the rate of postoperative liver failure to nearly zero percent (Figure 9, $P = 0.0113$). The low mortality rate shows that PVE not only decreased the occurrence of postoperative liver failure but provided a hepatic functional reserve.

Curative resection (R0), lymph node metastasis negative, tumor size smaller than 2 cm, well differentiated histology, and earlier tumor stage have been reported as favorable prognostic factors after resection for hilar bile duct cancer[17-19,38,66,98,100,102]. Combined vascular resection was not a prognostic factor, if curative resection was achieved[39-41,89]. Concomitant PD with hepatectomy did not significantly influence patient survival[17,18]. Therefore, extended radical resection for local advanced bile duct cancer has been justified only under the acceptable low mortality rate. On the other hand, patients with lymph node metastasis have had significantly poorer long-term results, and long-term survival has rarely been expected even when extended lymph node dissection was performed[34].

The reported five-year survival rates after PD for middle and distal bile duct cancer have ranged from 24% to 39%[20-22,24,37,103,104]. Curative resection, lymph node metastasis negative, intraoperative transfusion negative, well differentiated histology, and location (middle or distal) have been pointed out as a favorable prognostic factors for the treatment of middle and distal bile duct cancer. Sakamoto et al[24] emphasized the prognostic significance of the radical margin rather than hepatic margin in the treatment of middle and distal bile duct cancer. They insisted that significance of purchase to the negative hepatic margin is dependent on whether radical margin is negative for the tumor. Survival of patients with middle and distal bile duct cancer and lymph node metastasis is also poor, and Yeo et al[77] showed that radical extended lymph adenectomy provided no survival benefit in a randomized controlled trial. Nor have any studies shown a difference in survival between standard PD and PpPD[83-85].

CONCLUSION

Hemihepatectomy with or without pancreatoduodenectomy, plus extrahepatic bile duct resection and regional lymphadenectomy can be performed safely and offer a chance for cure of hilar bile duct cancer if preoperative BD followed by PVE is properly indicated. Major hepatectomy with PD and/or vascular reconstruction can be performed without mortality and results in improved resectability, curability, and a 5-year survival rate of 40%. PD is a standard procedure for middle and lower bile duct cancer, and the 5-year survival rate is nearly 30% with acceptable mortality rate. Radical resection with negative margins and no mortality is the goal of surgeons. Survival of patients with lymph node metastasis is still poor despite extended lymph node dissection, and to improve it is a future issue.

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