Changing trends of surgical treatment of hilar bile duct cancer: clinical and experimental perspectives

Zhi Qiang Huang, Ning Xin Zhou, Da Dong Wang, Jian Guo Lu and Ming Yi Chen

Huang ZQ, Zhou NX, Wang DD, Lu JG, Chen MY. Changing trends of surgical treatment of hilar bile duct cancer: clinical and experimental perspectives. *World J Gastroentero*, 2000;6(6):777-782

HISTORICAL POINT OF VIEW

Carcinoma of the confluence of the hepatic ducts has been thought to be a rare disease until recently. Carcinoma of the large hepatic ducts was rarely diagnose d correctly premorterned. Because of its deeply seated location, resection was once thought to be impossible. In 1957, Altemeier[1] reported 3 cases of sclerosing carcinoma of the major intrahepatic bile duct. One of the cases was operated upon for seven times within three years without a correct diagnosis until metastatic adenocarcinoma was found around the hepatic porta. However, this patient lived for three and half years after the first operation.

Klatskin[2] was the first one who drew attention to the hilar bile duct (HBD) carcinoma as a kind of tumor with definite clinical features. His paper was entitled as "Adenocarcinoma of the Hepatic Duct at its Bifurcation within the Porta Hepatis. An unusual tumor with distinctive clinical and pathological features" was reported in the *Am J Intern Med* in 1965. Thirteen cases, were analyzed from 1947-1963. Klatskin pointed out in his paper that "The purpose of this report is to draw attention to the unusual clinical and pathological features of adenocarcinom as that arise in the hepatic duct at its bifurcation within the porta hepatis". He laid emphasis on the fact that such type of tumor was often small-sized with a clear margin, metastasis has rarely been found, and the patient oft en died of prolonged biliary obstruction and liver failure

Research Institute of General Surgery, The General Hospital of PLA, Beijing 100853, China
Zhi Qiang Huang, graduated from the former National Zhong Zheng Medical College in 1944, now the academician of the Chinese Academy of Engineering, professor of surgery of the Postgraduate Military Medical College, Beijing, and the Director of the Research Institute of General Surgery, the General Hospital of PLA, Beijing
Correspondence to: Zhi Qiang Huang, Research Institute of General Surgery, General Hospital of PLA, 28 Fuxing Road, Beijing 100853, China
Tel. 0086-10-66939871, Fax. 0086-10-68181689
Received 2000-05-12   **Accepted** 2000-09-12

instead of tumor growth.

In our experience, slow progression of the tumor may be encountered very occasionally[3,4]. In our series of 157 cases of HBD carcinoma, we encountered a male patient of 61 years of age, who had received operation of insertion of endoprothesis because of jaundice about 5 years ago. After the operation, he developed repeated attacks of chills, fever and jaundice. We re-explored this patient and found that a well-localized tumor mass at the bifurcation of the hepatic duct, which was removed completely, and a cholangioenterostomy was created. Pathology of the resected tumor showed a highly differentiated adenocarcinoma of the confluence of the hepatic duct. The patient lived without recurrence for already 10 years since the last operation.

From January 1986 to January 1999, in the department of hepatobiliary surgery of our hospital 157 cases of hilar bile duct carcinoma (Table 1) were treated surgically. These experiences together with a series of experimental studies form the basis of this report[5-7].

Table 1 Surgical treatment of cases of hilar bile duct carcinoma (1986-1999 in this hospital)

Treatment	No. of patients	%
Resection	106	67.5
Radical resection	59	37.6
Biliary drainage	51	32.5
Total	157	100.0

TUMOR EXTENSION AND STAGING

The biliary tract is a continuous structure from its beginning as Hering's tubule to the lower part of the common bile duct. The exact confinement of Klatskin tumor has not been accurately defined. Therefore, many terms have been adopted for the description of the same or not the same conditions. Carcinomas arising from the intrahepatic small bile ducts are often called cholangioma, which is one of the primary liver tumors. But, as to those tumors arising from the larger intrahepatic duct near the hilum and invading the hepatic confluence at its late stage may be difficult to be differentiated from those arising from the hilar bile duct[8-10]. We are of the opinion that hilar bile duct cancer consisted of those cholangiocarcinomas of large bile ducts, which invaded the hepatic duct confluence[11,12].

There are many criteria for staging of hilar bile duct carcinoma such as those proposed by Bismuth-Corlette (1975)[13], Gazzanign (1993)[14] , pTNM (*Am J Co Cancer*), TNM (UICC), and the T-staging classification (Blumgart 1998)[9].

Bismuth and Corlette proposed the most widely used clinical pathological classification of hilar bile duct cancer in 1975[13]. However, this classification is of value only in defining the origin of the tumor. Clinically, when tumor originated from one of the hepatic ducts (Bismuth-Corlette Classification Type III), jaundice will not be an early symptom, and, in fact, it may a pear relatively late and clinical jaundice appeared only when tumor invaded the hepatic pedicle as the tumor advanced to the confluence of the hepatic duct to obstruct the opposite hepatic duct orifice[15]. Therefore, we often found that the tumor was unresectable in patients suffering from jaundice only for two weeks duration. In such cases, atrophy of one lobe (either the right or the left lobe) of the liver was present[16,17]. For staging of tumor progression, Gazzanign proposed a new staging criterion in 1993[14]. But it is difficult to exactly define the degree of tumor progression before operation. Recently, Blumgart (1998)[9] proposed a T-staging criteria which depends on the radiological features of tumor involvement of the portal vein and the presence of ipsolateral lobar atrophy in HBD cancer (Table 2). Since involvement of the portal vein is the chief independent risk factor in determining the resectability of bile duct cancer, therefore, it seems to be a simplified idea and is readily useful in clinical practice.

Table 2 T-staging of hilar bile duct cancer (Blumgart)[9]

T 1	No vessel involvement or liver atrophy
T 2	With ipsolateral liver atrophy
	No portal vein involvement
T 3	With ipsolateral portal vein involvement
	With or without associated liver atrophy
	No main portal vein involvement
T 4	Any of the followings
	Bilateral 2nd order hepatic duct involvement
	Main portal vein involvement

THE EVER-WIDENING CURATIVE RESECTION

Since the turn of the 1980s, in order to increase the radicality of tumor resection, radical resection of hilar bile duct cancer was proposed to include skeletalization of vascular structures of the liver pedicle, the combination of hepatic lobectomy, the wide dissection of regional lymph nodes, and even the inclusion of hepatobiliary pancreaticoduodenectomy[18-21].

The overall resectability rate of hilar bile duct cancer in China was rather low before 1985. In the Southwest Hospital, Chongqing, 60 surgical cases (1975-1985) of HBD cancer were explored with a resection rate of 8.3%. In a nationwide survey of surgical cases of extrahepatic bile duct cancer from 1978-1988 conducted by the Chinese Surgical Society, 422 surgical cases of hilar bile duct cancer were collected, the average resectability rate was about 10% (Table 3)[22]. This result was quite similar to the report from Bismuth (1960-1985) that in 178 cases with a resectability rate of 10%[13].

Table 3   Resectability of bile duct cancer in China (a nationwide survey, 1978-1988)

Location	No.patients	No.resected	%
Proximal	422	44	10.0
Middle	179	41	22.9
Lower	147	50	34.0
Total	748	135	18.0

However, after the year of 1985, more enthusiastic attitude was adopted in the surgical treatment of HBD carcinoma, which resulted in increase of resectability rate, and decrease of operative mortality rate. In our hospital from 1986 to 1990, 31 cases were resected among the 50 explored cases, with a resectability rate of 62%, and no 30-day postoperative death[23,24]. Similar trend of changes was also found in other hospitals in China[25].

However, the resectability rate varies which was much dependent on the policy of surgical intervention toward bile duct cancer. This differences may be partly due to the awareness of the disease and early diagnosis, and, even more important, the different attitude toward the choice of operative intervention in case of hilar bile duct carcinoma. In our hospital, we found that biliary drain age and stent placement by operative means had less late complications than that obtained by transcutaneous or transendoscopic route (Table 4). This finding was also confirmed by Guthrie[26] that operative intrahepatic biliary enterostomy of the III segmental duct carried a lower postoperative cholangitis than the percutaneously placed endoprothesis (19% and 55%, respectively). Therefore, we adopted the surgical therapy for all HBD cancer patients who are considered to be indicated for the operation.

Table 4 Biliary drainage and postoperative cholangitis in HBD cancer

Operation	No. of patients	No cholangitis(%)	Recurrent cholangitis(%)
Resection	59	74.6	25.4
Intern.drain.	11	36.4	63.3
Extern.drain.	21	52.4	47.6

The need of preoperative percutaneous transhepatic biliary drainage (PTBD) in jaundiced patients is still a debatable subject[27]. We used this approach in only one case when extended right

lobectomy was considered necessary. Recently, we planned a staged operation for a patient who needed a hepaticobiliary pancreaticoduodenectomy. We agreed with Nimura that preoperative biliary drainage is beneficial only in cases if extensive resection will be needed, and it should not be treated as a routine procedure[28]. We resected the caudate lobe of the liver only when the lobe was invaded by the tumor; otherwise, we transected the caudate segmental duct. In our experience, the hepatic artery, when encased by the tumor, may be excised en masse without harmful effect. Reconstruction of the portal vein after resection was undertaken under vascular control.

OUTCOME OF SURGICAL TREATMENT

During the 6th China National Biliary Surgical Conference held in Guangzhou in 1991, 139 cases of resection of HBD carcinoma were reported with a mortality rate of 0%-22%, being 5% on the average. The surgical treatment of HBD cancer of our hospital can be divided into two periods. The first period was from 1986 to 1993, during which 31 cases were resected with no 30-day postoperative death, 4 cases were living and tumor-free for more than 5 years (Table 5). During the second period, 32 cases were resected but no 5-year survival up to present (Table 6). Totally, from 1986 to 1999, 157 cases of HBD cancer were treated surgically in the General Hospital of PLA, Beijing, 106 of them were resected with a resectability rate of 67.5%, and 37.6% being considered radical resection (resection margins free of tumor cells). The 1, 3 and 5-year survival rate in the radical resection group was 96.7%, 23.3%, and 13.3%, respectively. In the palliative resection group (tumor cells present at one of the resection margins), no patient survived longer than 3 years[23]. But, in the recent 3 years (1996-1999), 40 (74%) of the 54 surgical cases of HBD carcinoma were resected, in which, 23 (57.5%) resections were considered radical. This represents the changing trends towards earlier operation in those patients.

Table 5　Tumor-free long-term survivals after radical resection of hilar bile duct carcinoma

Case	Sex	Age	Type	Histology	Operation	Follow-up
1	M	47	Nodular	Tubular Ca	B-D resection, lobectomy	6yr3mo
2	F	50	Papillary	Papillary Ca	B-D resection	7yr2mo
3	M	63	Nodular	Well dif.	B-D resection, Lt lobectomy	7yr10mo
4	M	53	Nodular	Well dif.	B-D resection	8yr3mo

B-D: bile duct; Ca: adenocarcinoma; Well dif.: well differentiated

Table 6　Survival rate of surgical treatment of hilar bile duct cancer (The General Hospital of PLA series, 1997)

Operation	n	1yr(%)	2(yrs)	3(yrs)	5(yrs)
Radical re	30	29(96.7)	12(40.0)	7(23.3)	4(13.3)
Palliative re	26	16(21.5)	2(7.7)	1(3.8)	0
Int. drainage	11	5(45.5)	0	0	0
Ext. drainage	23	6(26.1)	0	0	0

re: resection

At present, however, the late result of HBD cancer is still discouraging[29]. Boerma[30] reviewed the English literature published before 1990, resection of the tumor was obtained in 581 cases with an average mortality rate of 13%, the average survival period was 21 months, and the 1, 3 and 5-year survival rate was 67%, 22%, and 11% respectively. Recently, Nakeeb[31], from Johns Hopkins Medical Center, reported 109 cases resected with a 1, 3 and 5-year survival rate of 68%, 30% and 11%, and compared the cases treated with hepatic resection (n=15) with the cases without hepatic resection (n=94), which showed that there was no difference in the 1, 3 and 5-year survival rate, but the 5-year survival rate was better in those with negative margin (19%) than those with positive margin (9%). Nimura from Japan reported the result of a 5-year cure rate of 31% in 127 resected cases[28]. In the report from the Liver Transplantation Center in Pittsburg[32,33], 28 cases of HBD carcinoma underwent extensive resection including hepatic lobectomies and vascular reconstruction, the post-operative 30 days mortality rate was 24%,! but only one patient survived 5 years (Table 7).

Table 7 Survival rate after resection of hilar bile duct cancer (reported series)

Author	n	Rx (%)	Mortality rate (%)	Survival rate (%) 1yr	3yrs	5yrs
Pinson(1962-1983)[18]	156	16.0	4.0	84	44	36
Bismuth(1969-1990)[19]	122	18.9	0	87	25	
Tsuzuki(1973-1986)[21]	50	50.0	4.0	80	29	19
Cameron(1973-1989)[20]	96	40.6	2.6	70	27	11
Hadjis(1977-1985)[29]	131	20.6	7.4	70	26	22
Nimura(1977-1993)[28]	127	64.6	6.1	84	50	31
Boerma(1980-1989)*[30]	581	32.4	15.4	61	28	17
Zhou, Huang(1986-1996)[23]	103	34.9	0	96.7	23.3	13.3

Rx: radical resection; *:collected series

Therefore, Madariaga[33] from the Pittsburg group raised the question that the possible beneficial effect obtained through extensive operative procedure for HBD carcinoma is outweighed by the accompanying high morbidity and high mortality rate, so that the real significance of extensive surgery is questioned. Madariaga claimed that, for HBD carcinoma, it may be useless to prosuite for a cure resection as such is rarely possible, it may be encouraging to have a palliative resection if the operative morbidity and mortality rate can be kept much lower. We reach the same contention, that is, radical cure of hilar bile duct cancer is unlikely at present and should be left to those patients who may have an early diagnosis and early operation. But for most patients, efforts should be made to obtain a good palliative outcome with less postoperative complications.

Finally, we realized that carcinoma of the hilar bile duct, which rarely ran a "benign" course as described by Altemeier and Klatskin, is not an uniform disease, and is a regional disease rather than a local affection. It can metastase along the perineural space by a "jumping" fashion and invade adjacent tissue and blood vessels and lymphatics[34-36], therefore, surgical excision is bound to be unradical in the region of the porta hepatis for anatomical reasons.

EXPERIMENTAL STUDIES FOR FURTHER UNDER-STANDINGS OF HEPATIC HBD CANCER

Carcinoma of the hepatic duct bifurcation was considered a slowly growing malignancy and might have a better prognosis. However, from recent experience, this conclusion has been challenged. The long-term result of surgical resection of HBD carcinoma has been far from satisfactory. The 5-year survival rate of the radical resection group was from 13.3% to 17%[6,23]. Patients often died of local recurrence and hepatobiliary failure. Therefore, a research on the mode of recurrence in HBD carcinoma was undertaken by the author and his collaborators[35-39].

Coordinated clinical and pathological studies showed that metastasis of HBD cancer occurred rather early in the clinical cases. Therefore, in 32 cases of resections, metastasis was evidenced in 26 (83.9%) of the cases. The mode of spread was nerve invasion in 57.7%, direct liver invasion in 42.3%, soft tissue infiltration in 42.3%, liver metastasis in 7.7%, and lymph node metastasis was only found in one case (1.8%). Histologically, 21 (65.6%) of the 32 resected specimens were well-differentiated adenocarcinoma, 6 papillary adenocarcinomas, 3 were of low differentiation, and 2 carcinoma simplex[4].

Cholangiocarcinoma cells frequently metastased along the perineural lymph space. In 40 resected cholangiocarcinoma specimens, perineural space infiltration index (PNI) by cancer cells in relation to the median survival time was investi gated, the result showed a reverse correlation (Table 8).

Table 8   Neural infiltration index and median survival time

Differentiation of tumor cells	PNI*	Median survival time (mos)
Papillary	0.31±0.12	32
High	0.39±0.18	13.5
Moderate	0.74±0.39	10.8
Low	0.85±0.41	7.2

* PNI>7.0: severe nerve infiltration

In 78 surgical cholangiocarcinoma resection specimens (collected between 1989-1996), the significance of neural cell adhesion molecule (NCAM) in relation to clinicopathological findings was investigated, 68 of the 78 specimens showed nerve infiltration, blood vessels infiltration in 72, and lymphatic infiltration was present in 68. In 68 cases with neural infiltration, positive expression for NCAM was found in 51 cases. Furthermore, a reverse relationship was found between the positive NCAM expression and the degree of tumor cell differentiati on (Table 9)[40,41].

Table 9   Expression of NCAM and tumor differentiation

Cell type	NCAM Expression	
	(-)	(+)
Papillary	5	3
High diff.	10	12
Moderate diff.	8	16
Low diff.	3	21

$P=0.0267$, $\chi^2=9.20$

For further demonstration of spread of cholangiocarcinoma cell along the perineural space, observations of computer assisted 3 dimensional reconstruction of the pathological sections was made in 2 cases, totally 110-200 slides were selected for reconstruction using a SHOW 3D image analysis system. The results showed that a dense net-work of small vascular and lymphatic channels together with a branching net-work of tumor infiltrates are closely related along the nerve fiber. By using the "wire framing" technique to visualize the in terior structures, it was demonstrated that the tumor cells stayed in perineural space, lymphatics, and small vessels far from the primary focus of carcinoma. Probably, carcinoma cells involving a nerve at a place far from the original site must have reached there via lymphatics, vascular vessels or by direct invasion. These facts might be important in explaining the high recurrence rate of HBD carcinoma after conventional radical resection[42].

To investigate the relationship between hepatitis B and C virus infection of the bile duct mucosa and the occurrence of bile duct carcinoma, 51 excised bile duct cancer specimens from 1995 to 1998 were taken from the Department of Pathology, General Hospital of PLA, Beijing, for histochemical and IS-PCR studies. Five (9.8%) of the 51 cases of extrahepatic bile duct cancer (EBDC) showed positive reaction for HBsAg in the tumor tissue. Positive reaction was expressed as brownish granules in the cytoplasm of cancer cells, and no case was detected as inclusion bodies, membranous type, nor granules were seen in the nucleus or the cell membrane. A positive serum HBsAg was found in 3.9% of the 51 cases. Therefore, from this study, it was evident that HBV can infect the epithelial cells of the bile duct. In China, a positive rate of serum HBsAg was expected to be about 10% of the population. It may be concluded that, from pathological studies, HBV infection may not be strongly related with the

development of EBDC. However, as to the significance of HCV infection, the result may be on the contrary. Examination of the HCV NS_5 antigen in the 51 EBDC cases, 14(27.5%) showed positive expression in the cancer tissue. The pattern of antigen distribution in the cancer cells was similar to that of HBV granules, which was brownish granules distributed in the cell cytoplasm with no nucleus or cell membrane staining. Since the positive rate of anti-HCV was 0%-2.4%[43,44] in Chinese population, the positive rate of 27.5% found in the cancer tissue was much higher than the average, and may indicate a positive relationship between HCV infection and the development of EBDC[45,46]. This finding was in accordance with the recent report by Yin *et al*[47]. The mechanism of cancerous changes of HCV infected bile duct mucosal cells may be the consequence of bile duct cell destruction and hyperplastic proliferation.

Further study was made with in situ polymerase chain reaction (IS-PCR) in paraffin-embedded sections of 51 cases of EBDC, the results showed that 8 (15.9%) of the 51 cases was positive for HBV, the positive cells of HBV DNA were mainly clustered in the cancer tissue. In 2 cases, the brownish granules were exclusively located inside the nucleus of the cancer cells. Therefore, there is a rather high incidence of HBV infection in EBDC in spite of a negative serum test for HBsAg, and the integration of HBV DNA in the cell nucleus may play an important role in the carcinogenesis of EBDC.

Study of positive HCV RNA in the 51 cases of EBDC with IS-PCR revealed that 18 (35.4%) had detectable HCV RNA, of which, 15 were plus-strand RNA, and 3 were minus-strand RNA. Twelve detectable RNA was located in the cytoplasm, and 6 were in the nucleus. The positive cells of HCV RNA were mainly clustered in the cancer cells. Of 34 control specimens, only 2(5.9%) had detectable HCV RNA. These results suggested that HCV infection might be involved in the carcinogenesis of carcinoma of extrahepatic bile duct.

In recent years, studies of cancer pathogenesis have provided evidences that cancer is a disease developed through a process of cytogenetic disorders. It is now known that activation of proto-oncogen and inactivation of tumor suppressive gene are the most common genetic alternations in tumor, especially the loss of the function of tumor suppressive gene is considered as a key step in tumor progression. So the restoration of the function of tumor suppressive gene is a major approach for gene therapy for cancer. In recent years, attention has been focused on the *p*16 gene, which resides within a locus commonly deleted in established cancer lines (almost 75%).

In a series of 51 specimens of EHBC, we detected the expression of *p*16 gene so as to identify the relationship between the expression of *p*16 gene and the occurrence of metastasis and prognosis of the patients. Furthermore, we investigated the efficiency to transfer interest gene (Ad-p16, Ad-p53), cooperation of Ad-p16 with Ad-p53, Ad-p16 with CDDP and evaluated their inhibitory effect on human cholangiocarcinoma cell line QBC939[48] *in vitro* and Ad-p16 with CDDP *in vivo*. The results revealed that expression of *p*16 analyzed with S-P immunohistochemistry method, was found in 43.14% of the 51 EHBC, but the positive rate varied significantly in the pathological grading, nerve invasion, prognosis and option of surgical procedure (*P*<0.05).The growth rates of the Ad-p16-infected QBC939 cells were inhibited by 35.1% (8 days), and Ad-p53-infected QBC939 cells were inhibited by 24.4% (8 days). The growth rates of the Ad-p16-infected QBC939 cells with CDDP (0.5mg/L) were inhibited by 77.7%. The suppression effects mediated by expression of the exogenous p16 and p53 in tumor cell resulted mainly from apoptosis and GI arrest, while the suppression effects mediated by CDDP in tumor cell were mainly produced by apoptosis and G2 arrest. Experimental gene therapy on the nude mice model bearing subcutaneous tumor of QBC939 cells showed that intratumor instillation of Ad-p16 and intra-abdominal instillation of CDDP inhibited the growth of the tumors. The average size of the Ad-p16-treated, CDDP-treated or Ad-p16 with CDDP-treated tumors was inhibited by 30.0%, 41.0% and 62.6% respectively, as compared with that of the tumors injected with Ad-LacZ[49,50]. However, gene therapy of EHBD cholangiocarcinomama, as in most of the malignant tumors, still has a long way to go.

REFERENCES

1   Altemeier WA, Gall EA, Zinninger MM, Hoxworth PI. Sclerosing carcinoma of the major intrahepatic bile ducts. *AMA Arch Surg*, 1957;75:450-461
2   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
3   Huang ZQ. Surgical treatment of hilar bile duct carcinoma. *Zhonghua Waike Zazhi*,1990;28:522-526
4   Huang ZQ. Diagnosis and surgical treatment of biliary carcinoma. *Zhongguo Zhongliu*, 1999;8:414-416
5   Huang ZQ, Zhou NX, Liu YX, Li WH, Yu G. Surgical treatment of hilar bile duct carcinoma.Clinical and pathological studies. *Chin Med J*, 1992;105:635-640
6   Li WH, Huang ZQ, Zhou NX, Yu G, Liu YX. Clinical and pathological studies of hilar bile duct carcinoma. *Zhonghua Waike Zazhi*,1993; 31:536-538
7   Huang ZQ. New development of biliary surgery in China. *World J Gastroentero*, 2000;6:187-192
8   Huang ZQ. Strive for earlier diagnosis and treatment of hilar bile duct carcinoma.*Chin Med J*, 1992;105:619-621
9   Burke EC, Jarnagin WR, Hochwald SN, Pisters PWT, 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
10   Feydy A, Vilgrain V, Denys A, Sibert A, Belghiti J, Vullierme MP, Menu Y. Helical CT assessment in hilar cholangiocarcinoma: correlation with surgical and pathologic findings. *AJR*, 1999;172:73-77
11   Huang ZQ. Biliary surgery in China: progress in the past fifty years. *Chin Med J*, 1999;112:897-900

12 Huang ZQ. Changing viewpoint of surgical treatment of hilar bile duct carcinoma. *Xiaohua Waike*, 1999;1:5-9

13 Bismuth H, Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. *Surg Gynecol Obstet*,1975; 140:170-178

14 Gazzaniga GM, Filauro M, Bagarolo C, Ciferri E, Bondanza G. Neoplasm of the hepatic hilum: the role of resection. *Hepatogastroenterology*, 1993;40:244-248

15 Huang ZQ. Measures to improve the result of surgical treatment of hilar bile duct carcinoma. *Zhongguo Shiyong Waike Zazhi*, 1998; 18:325-326

16 Chen MF, Jan YY, Chen TC. Clinical studies of mucin-producing cholangiocellular carcinoma. *Ann Surg*, 1998;227:63-69

17 Kuszyk BS, Soyer P, Bluemke DA, Fishman EK. Intrahepatic cholangiocarcinoma: the role of imaging in detection and staging. *Crit Rev Diag Imag*, 1997;38:59-88

18 Pinson CW, Rossi RL. Extended right hepatic lobectomy, left hepatic lobectomy, and skeletonization resection for proximal bile duct cancer. *World J Surg*, 1988;12:52-59

19 Bismuth H,Nakache R,Diamond T.Management strategies in resection for hilar cholangiocarcinoma. *Ann Surg*,1992;215:31-38

20 Cameron JL, Pitt HA, Zinner MJ, Kaufman SL, Coleman J. Management of proximal cholangiocarcinomas by surgical resection and radiotherapy. *Am J Surg*, 1990;159:91-98

21 Tsuzuki T, Ueda M, Kuramochi S, Iida S, Takahashi S, Iri H. Carcinoma of the main hepatic duct junction: indications, operative morbidity and mortality, and long-term survival. *Surgery*, 1990;108:495-501

22 Zhou NX, Huang ZQ, Liu YX, Li SX. A national survey of 1098 cases with extrahepatic cancer. *Zhonghua Waike Zazhi*, 1990; 28:516-521

23 Zhou NX, Huang ZQ, Feng YQ, Gu WQ, Cai SW, Zhang WZ, Huang XQ, Duan YP, Wang J, Ji WB. The long-term results of surgical treatment in 103 cases of hilar cholangiocarcinoma. *Zhonghua Waike Zazhi*, 1997;35:649-653

24 Huang XQ, Cai SW, Zhou NX, Feng YQ, Huang ZQ. Prevention of acute renal failure after surgical resecting hilar bile duct carcinoma. *Waike Lilun Yu Shijian*, 1999;4:55-56

25 He XS, Huang JF, Liang LJ, Lu MD, Cao XH. Surgical resection for hepatoportal bile duct cancer. *World J Gastroentero*, 1999;5:128-131

26 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

27 Takada T, Yasuda H. Value of pre-operative biliary drainage prior to bile duct cancer surgery: results of a retrospective review. *Asian J Surg*, 1996;19:84-87

28 Nimura Y, Hayakawa N, Kamiya J, Kondo S, Nagino M, Kanai M. Hepatectomy for hilar bile duct cancer. *Asian J Surg*, 1996;19: 94-100

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

30 Boerma EJ. Research into the results of resection of hilar bile duct cancer. *Surgery*, 1990;108:572-580

31 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;224:463-475

32 Iwatsuki S, Todo S, Marsh JW, Madariaga JR, Lee RG, Dvorchik I, Fung JJ, Starzl TE.Treatment of hilar cholangiocarcinoma (Klatskin tumors) with hepatic resection or transplantation. *J Am Coll Surg*, 1998;187:358-364

33 Madariaga JR, Iwatsuki S, Todo S, Lee RG, Irish W, Starzl TE. Liver resection for hilar and peripheral cholangiocarcinomas: a study of 62 cases. *Ann Surg*, 1998;227:70-79

34 Ogura Y, Kawarada Y. Surgical strategies for carcinoma of the hepatic duct confluence. *Br J Surg*, 1998;85:20-24

35 Kurosaki I, Tsukada K, Hatakeyama K, Muto T. The mode of lymphatic spread in carcinoma of the bile duct. *Am J Surg*, 1996;172:239-243

36 Sakamoto E, Nimura Y, Hayakawa N, Kamiya J, Kondo S, Nagino M, Kanai M, Miyachi M, Uesaka K. The pattern of infiltration at the proximal border of hilar bile duct carcinoma. *Ann Surg*, 1998;227:405-411

37 Chen RF, Zou SQ. A study on the relationship between vascular endothelial growth factor and angiogenesis in hilar cholangiocarcinoma. *Zhonghua Putong Waike Zazhi*,2000;15:340-342

38 Yang ZL, Li YG, Zhong DX, Zhuang ZG, Lu F. Quantitative analysis of blood capillary in the tissue of bile duct carcinoma and its implication. *Zhonghua Shiyan Waike Zazhi*,1995;12:201

39 Chen RF, Sun HW, Tong YX, Zou SQ. Inhibition of VEGF expression by antisense oligodeoxynucleotides in cholangiocarcinoma. *Zhonghua Shiyan Waike Zazhi*, 2000;17:14-15

40 Wang DD, Huang ZQ, Zhou NX, Chen LZ. The role of neural cell adhesion molecule in perineural invasion of cholangiocarcinoma. *Zhonghua Shiyan Waike Zazhi*, 2000;17:171-172

41 Wang DD, Huang ZQ, Wang JX, Wang YS, Chen LZ. Relationship between perineural invasion and the coupling expression of DPC4 with NCAM in cholangiocarcinoma. *Zhonghua Shiyan Waike Zazhi*, 2000;17:12-14

42 Wang DD,Huang ZQ,Zhou NX,Chen LZ,Dai P.Three dimensional reconstructing neural invading model of cholangiocarcinoma. *Zhonghua Waike Zazhi*, 2000;38:207

43 Wang WL, Gu GY, Hu M, Wang CJ. Expression and significance of genes and HBV in human primary intrahepatic cholangiocarcinoma. *Huaren Xiaohua Zazhi*, 1998;6:1039-1042

44 Tao QM, Wang Y, Wang H, Chen WR, Sun Y, Meng Q. Investigation of anti-HCV in 391 serum samples in China. *Chin Med J*, 1990;103:616-618

45 Chen MY, Huang ZQ, Chen LZ, Gao YB, Peng RY, Wang DW. Detection of HBsAg and HCV NS 5 antigen in the tissue of extrahepatic bile duct cancer. *Junyi Jinxiu Xueyuan Xuebao*, 2000;21:116

46 Huang ZQ. A glimpse of hepato biliary pancreatic surgery in China. *Chin Med J*, 1998;111:1059

47 Yin FZ, Chen BF. Detection of hepatitis C virus RNA sequences in hepatic portal cholangiocarcinoma tissue by reverse transcription polymerase chain reaction.*Chin Med J*, 1998;111:1068-1070

48 Wang SG, Han BL, Duan HC, Chen YS, Peng ZM. Establishment of extrahepatic bile duct cancer cell line. *Zhonghua Shiyan Waike Zazhi*, 1997;14:67-68

49 Lu JG, Huang ZQ, Wu JS, Wang Q, Ma QJ, Yao X. Significance of tumor suppressor gene *p*16 expression in primary biliary cancer. *Shijie Huaren Xiaohua Zazhi*, 2000;8:638-640

50 Lu JG, Lin C, Huang ZQ, Wu JS, Fu M, Zhang XY, Liang X, Yao X, Wu M. Inhibitory effects of human cholangiocarcinoma cell line by recombinant adenoviruses p16 with CDDP. *Shijie Huaren Xiaohua Zazhi*, 2000;8:641-645

Edited by Ma JY