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

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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 diagnosed correctly premortem. 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 hepatitis”. 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 often died of prolonged biliary obstruction and liver failure 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].

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
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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\(^{[3]}\). 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 appear relatively late and clinical jaundice appeared only when tumor invaded the hepatic pedicle as the tumor advanced to a state of invasion. 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.

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

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

T1 No vessel involvement or liver atrophy
T2 With ipsolateral liver atrophy
T3 With ipsolateral portal vein involvement
T4 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. of 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\(^{[13,34]}\). 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 endoprosthesis (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 hepaticobiliopancreaticoduodenectomy. 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 diff. | B-D resection, Lt lobectomy | 7yr10mo |
| 4    | M   | 53  | Nodular | Well diff. | B-D resection | 8yr3mo |

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

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

| Operation | n | 1yr (% | 2yrs | 3yrs | 5yrs |
|-----------|---|--------|------|------|------|
| Radical re | 30 | 29(96.7) | 12(40.0) | 7(23.3) | 4(13.3) |
| Palliative re | 26 | 16(61.5) | 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 |

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

| Author | n | Rx (%) | Mortality rate (%) | Survival rate (%) |
|--------|---|--------|--------------------|-------------------|
| Pinson(1962-1983)[28] | 156 | 16.0 | 4.0 | 84 |
| Bismuth(1969-1990)[28] | 122 | 18.9 | 0 | 87 |
| Tsuzuki(1973-1986)[29] | 50 | 50.0 | 4.0 | 80 |
| Cameron(1973-1989)[29] | 96 | 40.6 | 2.6 | 70 |
| Hadjis(1977-1985)[29] | 131 | 20.6 | 2.6 | 70 |
| Nimura(1977-1993)[29] | 127 | 64.6 | 6.1 | 84 |
| Boerma(1980-1988)[29] | 581 | 32.4 | 15.4 | 61 |
| Zhou, Huang(1996-1999)[29] | 103 | 34.9 | 0 | 96 |

Rx: radical resection; *collected series

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).

Therefore, Madariaga[31] 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 metastasize along the perineural space by a “jumping” fashion and invade adjacent tissue and blood vessels and lymphatics[14-30], therefore, surgical excision is bound to be unradical in the region of the porta hepatitis for anatomical reasons.

**EXPERIMENTAL STUDIES FOR FURTHER UNDERSTANDINGS 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[18-19].

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 metastasized 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).

| 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 differentia tion 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
In a series of 51 specimens of EHBC, we detected the expression of p16 gene so as to identify the relationship between the expression of p16 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 in vitro and Ad-p16 with CDDP in vivo. The results revealed that expression of p16 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. However, gene therapy of EHBD cholangiocarcinoma, as in most of the malignant tumors, still has a long way to go.

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