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Surgical treatment of hepato-pancreato-biliary disease in China: the Tongji experience

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Hepato-pancreato-biliary (HPB) tumors are common in China. However, these tumors are often diagnosed at intermediate/advanced stages because of the lack of a systemic surveillance program in China. This situation creates many technical challenges for surgeons and increases the incidence of postoperative complications. Therefore, Dr. Xiao-Ping Chen has made many important technical improvements, such as Chen's hepatic portal occlusion method, the anterior approach for liver resection of large HCC tumors, the modified technique of Belghiti's liver-hanging maneuver, inserting biliary-enteric anastomosis technique, and invaginated pancreaticojujunostomy with transpancreatic U-sutures. These techniques are simple, practical, and easy to learn. Owing to these advantages, complicated surgical procedures can be simplified, and the curative effects are greatly improved. These improved techniques have been widely applied in China and will benefit many additional patients. In this review, we introduce our experience of surgically treating intermediate/advanced hepatocellular carcinoma (HCC), hilar cholangiocarcinoma (HC), and pancreatic carcinoma, mainly focusing on technical innovations established by Dr. Chen in HPB surgery.

hepatocellular carcinoma, liver transplantation, hilar cholangiocarcinoma, pancreaticojejunostomy

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INTRODUCTION

Hepato-pancreato-biliary (HPB) tumors are very common diseases in China. These tumors are usually aggressive and have poor prognosis. Surgery is the only potential curative therapy for these malignancies. The most common form of tumor in the liver is hepatocellular carcinoma (HCC), which commonly results from hepatitis B virus infection and is prone to be diagnosed at intermediate/advanced stages owing to the lack of a systemic surveillance program in China. Intermediate/advanced HCC, particularly a huge HCC tumor, creates many technical challenges for surgeons. Hilar cholangiocarcinoma and pancreatic head carcinoma are extremely malignant tumors, which usually cause obstruction of the bile duct, leading to deterioration in the patient's general condition. Surgery is technically challenging for these tumors. Therefore, technical innovations for surgical treatment of these malignant tumors are urgently needed to improve the operative safety and long-term outcomes of these diseases in China.

A recent national survey in China (unpublished data, research code 201043901), involving 75 hospitals and 30,536 patients with HCC, found that 43.1% of patients had a tu-

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mor larger than 5 cm and 22.5% had a tumor larger than 10 cm in diameter at their first visit to a doctor. About one-third of patients with a large HCC tumor displayed portal hypertension or invasion of the portal vein by the tumor. In such cases, nonsurgical treatment, such as transcatheter arterial chemoembolization (TACE) and/or systemic treatment, results in poor long-term survival rates. However, studies have shown that liver resection improves the long-term survival of patients with large HCC tumors or intermediate/advanced HCC. Over the past few decades, liver resection for HCC has evolved to become safe, with a low operative mortality rate, and at the Hepatic Surgery Center of Tongji Hospital, liver resection is routinely recommended to patients with large HCC tumors, irrespective of the size of the tumor or the presence of portal hypertension or portal vein tumor thrombosis (PVTT). Patients who undergo surgery show significant improvements in their long-term survival rate compared with patients who receive non-surgical treatment.

Malignancies at the hepatic hilus and the head of the pancreas have poor prognoses. Surgery is the only possible curative treatment that may prolong survival. However, the rate of postoperative complications is very high. Bile duct or pancreas reconstruction with intestine is the major intraoperative difficulty as well as the main reason for postoperative complications, including bleeding, infection, liver failure, bile leakage, and pancreatic fistula. Chen recommends minor hepatic resection and applies an inserting biliary-enteric anastomosis technique for HC. The long-term survival was comparable, while postoperative complications were significantly reduced. For pancreatic cancer, we used Chen's invaginated pancreaticojejunostomy with transpancreatic U-sutures, a simple technique that reduced postoperative pancreatic fistula (POPF).

Owing to his outstanding contribution to HPB surgery, Dr. Chen had been elected as an academician of the Chinese Academy of Science in 2015. This review is mainly focused on Chen's major contribution to HBP surgery.

HEPATOCELLULAR CARCINOMA

Large hepatocellular carcinoma

Although there is no universally accepted definition of a large HCC tumor, we have defined it as a tumor greater than 5 cm in diameter; a "huge" HCC tumor is deemed to be a tumor greater than 10 cm in diameter. A significant proportion of patients present with large HCC tumors at initial diagnosis in our institution. The 5-year survival rates after liver resection range from 28% to 42% for HCC tumors >5 cm and from 17% to 32% for HCC tumors $\geqslant$10 cm; these results are significantly superior to the 5-year survival rates after TACE. Unfortunately, liver resection in a patient with a large HCC tumor is associated with a high risk of post-operative liver failure and a significantly high recurrence rate. Post-operative morbidity rates range from 27% to 33.8%, mortality rates range from 2.4% to 6.0% and 5-year recurrence-free survival rates range from 20% to 26% (Zhong et al., 2014).

Chen believes that hepatectomy for large or huge HCC removes relatively less normal liver parenchyma, while hepatectomy for small HCC removes more normal liver parenchyma (Chen, 1994). The remnant liver parenchyma in the tumor located lobe is relatively reduced due to pressure or destruction by the tumor, while the healthy liver lobe undergoes compensative proliferation as a result. Therefore, the remnant liver is possibly sufficient even after removing the huge HCC. With advances in surgical techniques, large or huge HCC tumors are no longer a contraindication to liver resection. From January 1990 to December 2003, 2,102 patients with large HCC tumors underwent liver resection at our center (Chen et al., 2006a). These patients were divided into two 7-year periods: before the end of December 1996 and after December 1996. The 5-year disease-free and overall survival rates were 23.8% and 38.7%, respectively, in group 2, and 18.9% and 27.9%, respectively, in group 1. This study demonstrated that liver resection in patients with large HCC tumors can result in good long-term outcomes.

The incidence of post-hepatectomy liver failure is closely correlated with the volume and function of the remnant liver. Liver resection in a patient with a large HCC tumor generally involves the removal of the tumor along with the surrounding liver parenchyma. Compensatory hypertrophy usually occurs in the contralateral liver, even in the presence of cirrhosis, thus supporting the use of major resection in patients with large or even huge HCC tumors. A systematic review found that 50.9%–96.2% of patients with a huge HCC tumor are treated by major resection, and this figure is 76.3% at our center. When selecting patients with large HCC tumors for liver resection, accurate evaluations of liver functional reserve and remnant liver volume are essential; the Child-Pugh classification alone is not sufficient to define the safe limit of extent of liver resection. At our center, liver resection for a huge HCC tumor is only performed in the presence of good cardiopulmonary and renal functions, Child-Pugh grade A, and a retention rate of indocyanine green at 15 min (ICG-R15) of less than 15% (Chen et al., 2006a). Computed tomographic (CT) volumetry is also used in determining whether the remnant liver volume is adequate. A combination of CT volumetric measurement and ICG-R15 can provide a better index for selecting patients for major liver resection. Recently, we retrospectively studied 996 patients with chronic hepatitis B or C who underwent liver resection for HCC and found that total cholesterol level was significantly correlated with post-operative complications. Patients with low cholesterol level ($<$2.8 mmol L^{-1}) had worse pre-operative liver functional reserves and had more post-operative complications than patients with normal cholesterol levels ($\geqslant$2.8 mmol L^{-1})

(Wang et al., 2014).

Resection of a large HCC tumor is technically challenging, especially if the tumor is in the right side of the liver and is larger than 10 cm. A large tumor also poses difficulties in the control of hepatic veins before or during liver transection. Thus, patients with a large HCC tumor tend to have more intra-operative blood loss, more blood transfusions, and longer operation time. Since 1987, our center has implemented the anterior approach (parenchymal transection without prior mobilization of the liver) for liver resection of a large HCC tumor. Pringle's maneuver is routinely used to occlude the hepatic inflow. For difficult hepatectomies, the hepatic pedicle and the inferior vena cava below the liver are clamped simultaneously for better hepatic vascular inflow and outflow control (Chen's method). The liver parenchyma is transected using a finger-fracture technique in the early period. Up-to-date instruments are used, such as the BiClamp, cavitron ultrasonic surgical aspirator (CUSA), microwave coagulator, ultrasonic scalpel, water-jet dissector, and ligasure vessel sealing system. After splitting the liver in the midplane, the liver is then mobilized by dividing the ligaments. This resection method avoids laceration of major vessels during early liver mobilization as well as the rupture of large tumors owing to excessive traction. In addition, delaying liver mobilization until near the end of the operation prevents excessive bleeding from retroperitoneal venous collaterals that have opened up in patients with cirrhosis and portal hypertension. Importantly, this resection method follows the oncological principle of a no-touch technique by ligating vessels before the excessive handling of tumors, thus minimizing shedding of tumor cells into the bloodstream and preventing metastatic seeding. Patients with a large HCC tumor who are treated with liver resection using this method have significantly better long-term outcomes.

Dr. Chen has established several techniques for liver resection in patients with a large HCC tumor. For anatomical right or left hemihepatectomy, a simple technique has been developed by directly ligating the corresponding inflow and outflow pedicles of the hemiliver to be resected without prior hilar dissection. He has also established a liver double-hanging maneuver that is a modification of Belghiti's liver-hanging maneuver (Figure 1). Recently, these techniques have been applied to laparoscopic hepatectomy and da Vinci robotic hepatectomy at Tongji Hospital. His method is an improvement because the tunnel is set up through a retrohepatic avascular plane on the right of the inferior vena cava. It is easy to perform and has a high success rate and a low chance of inducing bleeding when making the tunnel. With the use of these effective methods, our operative mortality is now 0.7%, compared with 2.4%–6.0% in other large HCC series.

Multiple hepatocellular carcinoma

According to the Barcelona Clinic Liver Cancer (BCLC) staging system and treatment recommendations, TACE is the treatment of choice for multiple HCC tumors (except when there are fewer than three tumors and they are each smaller than 3 cm in diameter, in which case the treatment recommendation is liver transplantation or ablation with percutaneous ethanol injection (PEI) or radiofrequency ablation (RFA). However, the long-term outcomes of TACE treatment in such cases are dismal.

Liver resection in patients with multiple HCC tumors remains controversial. In Western countries, liver resection is usually indicated for a solitary HCC tumor because resection of multiple tumors carries a high recurrence risk and results in unfavorable survival outcomes. In contrast, liver resection for multiple tumors has been attempted in up to 20% of all liver resections for HCC at our center (Chen et al., 2006a). Despite the increased risk of recurrence in patients with multiple lesions, the evidence suggests that liver resection is justified in carefully selected patients. Several surgical series on a small number of patients with large and multiple HCC tumors have reported a median survival ranging from 9.8 to 12 months. Thus, in the era of modern surgery, with appropriate patient selection, even multiple HCC tumors are not a contraindication for liver resection.

For multiple tumors, liver resection usually needs to be combined with local ablative therapies to destroy tumors in the contralateral hemiliver. The strategies for treating multiple tumors at our center include *en bloc* resection of all tumors in one hemiliver; resection of a large tumor in one hemiliver combined with wedge resection of a smaller le-

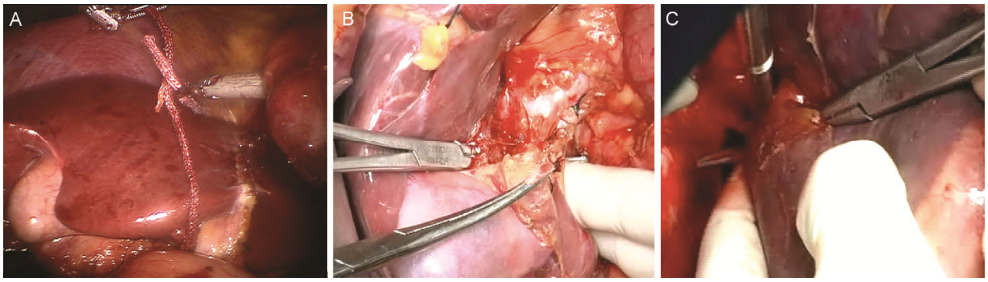

Figure 1 (Color online) Liver double-hanging maneuver and a simple technique for ligating of inflow and outflow vessels without hilar dissection during hepatectomy. A, Chen's modified liver double-hanging maneuver in da Vinci robotic hepatectomy. B and C, Ligation of inflow and outflow vessels without hilar dissection during anatomical right hepatectomy. B, Ligation of the right hemihepatic pedicle. C, Ligation of the right hepatic vein.

sion; or local ablation of centrally or deeply located tumors in the other hemiliver. Combining local ablation with liver resection has been found to be a safe and effective strategy to treat multiple HCC tumors.

Multiple HCC tumors may result from multicentric occurrence (MO) or intrahepatic metastasis (IM). Studies have suggested that IM occurs more commonly from tumors with PVTT, in multiple satellite nodules surrounding a main tumor or when a satellite tumor near a main tumor shows similar or poorer histological differentiation when compared with the main tumor. Multiple HCC tumors that do not meet these criteria are more likely to result from *de novo* MO. The prognosis after liver resection for HCC with MO is usually better than for HCC with IM. Thus, HCC with synchronous or metachronous MO represents an indication for liver resection. Discrimination of IM and MO is important because, in general, HCC that has acquired metastatic ability exhibits more aggressive biological behavior, thus influencing therapeutic strategy decisions. Molecular biological studies are the only way to be certain that multiple HCC tumors have MO or IM origin. More studies should be conducted aiming to differentiate IM from MO to further improve surgical outcomes.

Hepatocellular carcinoma with portal vein tumor thrombosis

HCC tends to invade adjacent venous tributaries, which is associated with an increased risk of intrahepatic or extrahepatic metastases. PVTT (including thrombosis in the secondary/primary portal branches or the main portal trunk) is present in 5.3%–15.4% of patients undergoing liver resection, 11.3%–38.0% of patients receiving non-surgical treatment and 32.0%–62.2% of autopsy cases (1994). PVTT is the most predictive factor of poor survival in patients with HCC. According to the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) guidelines for HCC management, patients with PVTT are not candidates for either surgical treatment or TACE, and only palliative therapies are recommended. The median survival rate for untreated HCC with PVTT is 2.7 months (Llovet et al., 1999). TACE only achieves 5-year survival rates of 0%–6.1% for HCC with PVTT, and the outcomes of other non-surgical treatments, including sorafenib, are disappointing (Chen et al., 2006b; Llovet et al., 1999). Previous studies have shown liver resection to be a safe and effective treatment for HCC with PVTT if patients are carefully selected. In a retrospective series at our center including 438 patients with HCC and PVTT who underwent liver resection, the 1-, 3- and 5-year survival rates were 52.1%, 16.0% and 11.8%, respectively (Chen et al., 2006b). If only patients with PVTT in the primary or secondary branches of the main portal trunk were considered, the 1-, 3-, and 5-year overall survival rates were 58.7%, 22.7%, and 18.1%, respectively (Figure 2).

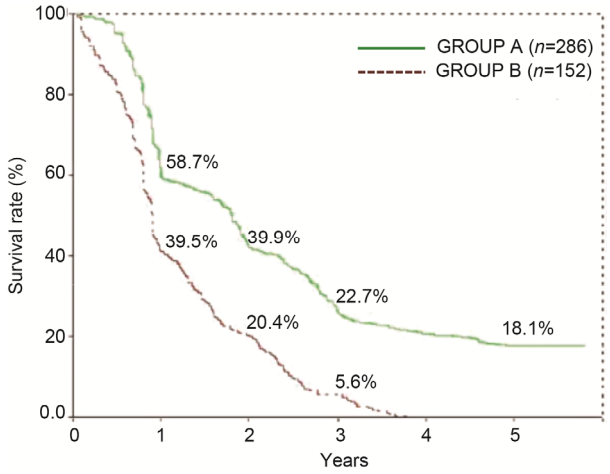

Figure 2 (Color online) Survival curves showing the overall survival rates of group A (PVTT was located in the hepatic resection area or protruded into the first branch of the main portal vein beyond the resection line for <1 cm) and group B (PVTT extended into the main portal vein). A significant difference is observed between the two curves (log-rank test; P<0.0164) (Chen et al., 2006b).

It has now been generally accepted in Asian countries that when PVTT is confined to the primary branch of the main portal trunk, the tumor and PVTT can be completely removed by liver resection, with resection of the ipsilateral portal vein branch containing the tumor thrombus. When the tumor thrombus has extended to the main portal trunk, surgical resection is usually not considered. However, our experience shows that concomitant liver resection and thrombectomy can safely be performed in selected patients with HCC and PVTT extending to the main portal trunk, provided that the patients have preserved liver function and the tumors are resectable; such operations have 1-, 2-, and 3-year overall survival rates of 39.5%, 20.4%, and 5.7%, respectively. Although concomitant liver resection and thrombectomy is a palliative treatment, it still offers substantial benefit in selected patients with HCC and tumor thrombosis in the main portal trunk. Liver resection in such patients may provide the following benefits: decreased portal venous pressure, improved liver function, prolonged survival, and improved quality of life.

Hepatocellular carcinoma with portal hypertension

The surgical indications for patients with HCC and portal hypertension remain controversial. Based on the BCLC staging system and the National Comprehensive Cancer Network (NCCN) guidelines for treatment of HCC, liver resection is contraindicated in patients with portal hypertension, as this condition is associated with a high incidence of post-operative liver decompensation and a poor survival rate. Recently, some authors have been advocating liver resection for patients with HCC and portal hypertension. The reported 5-year overall survival rates after liver resection vary from 25% to 51.5% in patients with portal hyper-

tension and from 50% to 70% in patients without portal hypertension. Our retrospective clinical study also provided important evidence that selected HCC patients with PHT could benefit from hepatic resection as compared with TACE or thermal ablation (Xiao et al., 2015).

In China, 85%–90% of patients with HCC show various degrees of liver cirrhosis, and a large proportion of these patients present with clinical signs of portal hypertension. The potential risks of liver resection in patients with portal hypertension are liver decompensation, peri-operative variceal bleeding, and hemostatic disorders. To avoid these complications, at Tongji Hospital we routinely perform pre-operative upper gastrointestinal endoscopy to evaluate the risk of variceal bleeding and to limit the extent of liver resection. In selected patients, we perform splenectomy with or without devascularization of gastroesophageal varices.

Our strategy for dealing with patients with HCC and cirrhotic hypersplenism is different from that of other centers. Usually, for patients with resectable HCC with splenomegaly and hypersplenism, splenicarterial embolization is the treatment of choice to reduce splenic size and to control hypersplenism so that liver resection can safely be performed. Some authors suggest that laparoscopic splenectomy should be carried out as a preliminary procedure to a second-stage liver resection. However, these two-stage operations may cause complications and prolong hospital stay. To solve this problem, we conducted a study in patients with resectable HCC and hypersplenism in order to compare the outcomes of simultaneous liver resection and splenectomy (the LS group) with those of liver resection only (the L group). There was no surgical death in either of these groups, and there was no significant difference in the incidences of complications. Patients in the LS group had a significantly higher 5-year recurrence-free survival rate compared to the L group (37.2% vs. 27.2%). There was no significant difference in overall 5-year survival rates between the two groups (Chen et al., 2005) (Figure 3).

These data indicate that not only is it safe to use simultaneous liver resection and splenectomy to treat patients with HCC and hypersplenism, this approach is therapeutically superior to liver resection alone. When an enlarged spleen associated with hypersplenism is removed, white blood cells and platelet counts return to normal levels; this favors the use of post-operative adjuvant chemotherapy, which may help to decrease tumor recurrence and might account for a lower recurrence-free survival rate in the LS group. Furthermore, simultaneous liver resection and splenectomy does not weaken the patients' immunological function; on the contrary, it is associated with homeostasis of T cell subsets and T helper 1 cytokines in the early post-operative period. Therefore, the immunological function in patients with HCC might be improved following splenectomy, which might contribute to a better antitumor immunological function and a decreased tumor recurrence rate.

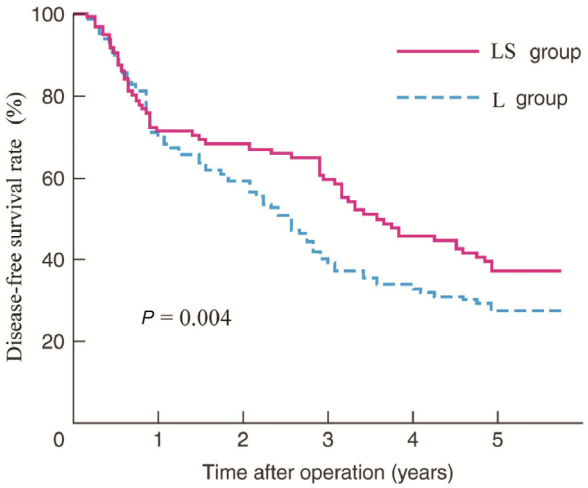

Figure 3 (Color online) Disease-free survival curves of patients with hepatocellular carcinoma undergoing liver resection and splenectomy (the LS group) or liver resection alone (the L group). (Chen et al., 2005).

Although liver resection in association with splenectomy with or without devascularization of gastroesophageal varices can be performed safely in patients with HCC and portal hypertension, these complex procedures are likely to lead to post-operative complications, particularly post-operative liver failure, because patients with cirrhosis tend to have poor liver functional reserve. As a consequence, the decision whether to perform liver resection or concomitant liver resection and splenectomy in patients with HCC and portal hypertension should be made very carefully. To ensure the safety of resection in patients with HCC and portal hypertension, we pay special attention to evaluating the preoperative liver function by using the ICG-R15 test, CT volumetry of the remnant liver, and the severity of cirrhosis. In patients with severe cirrhosis, limiting the extent of resection by non-anatomic resection is an effective way to prevent post-operative liver failure.

Recurrent hepatocellular carcinoma

The incidence of recurrence after liver resection is extremely high. The 5-year cumulative recurrence rates are 77%–100%, and 80%–95% of recurrences are confined to the remnant liver (Huang et al., 2012). Effective therapeutic strategies for intrahepatic recurrence are critical in prolonging survival after liver resection. The treatment algorithm for recurrent HCC varies, and no consensus has been reached. Treatment modalities for recurrent HCC include TACE, ablation therapy, repeat liver resection, salvage liver transplantation, and medical treatment. TACE is applicable to almost all patients with intrahepatic recurrences, and it plays an important role in the treatment of multiple recurrent HCC tumors. However, it is a palliative treatment, and long-term survival cannot be expected. Percutaneous ablation therapies, such as PEI, RFA, and microwave coagula-

tion therapy (MCT) also play important parts in the management of recurrent HCC. RFA has been increasingly used as the preferred percutaneous therapy because of its effective local tumor control. Several studies showed that RFA achieved long-term outcomes similar to those of repeat liver resection in the treatment of intrahepatic recurrence after initial liver resection, especially in patients with no more than three recurrent tumor nodules of less than 3 cm in diameter (Lau and Lai, 2009). RFA can be performed percutaneously, and its high repeatability renders it a preferred treatment option in selected patients with HCC recurrence. Recently, MCT has been reported to yield results similar to RFA for small recurrent HCC tumors. At our center, RFA and MCT are recommended for recurrent tumors smaller than 3 cm each and numbering three or less, situated deep in the liver.

Repeat liver resection is also a good alternative treatment for recurrent HCC if a patient's liver function is good. The 5-year survival rate after repeat liver resection varies from 23% to 69% in different studies, suggesting that repeat liver resection results in good outcomes in selected patients (Huang et al., 2012). However, the selection criteria of repeat liver resection for recurrent HCC remain vague and controversial. Some studies suggest that repeat liver resection is the treatment of choice for patients who have solitary recurrent HCC, who develop recurrence after a recurrence-free period of 1 year or more, and who show no vascular invasion (Minagawa et al., 2003). Surgeons have recently recognized that the types of HCC recurrence—that is, either metastases from a primary HCC (IM) or the development of new HCC foci (MO) as a consequence of persistent chronic active hepatitis and/or cirrhosis after liver resection—are the most important indicators for predicting long-term survival (Huang et al., 2012). Our study on the recurrent types of HCC revealed that repeat resection resulted in better outcomes in patients with the MO type than in patients with the IM type (Huang et al., 2012). The 5-year overall survival rate after repeat resection for MO patients with recurrent HCC tumors of $\leqslant$5 cm was up to 56%. This survival rate was similar to that for patients with small HCC tumors after initial resection in other studies. However, for the IM patients with recurrent HCC tumors of $\leqslant$5 cm, the 5-year overall survival rate after repeat resection was only 8%. With close supervision after the initial resection, most recurrent HCC can be diagnosed at an early stage. Considering that only MO patients can expect a significant survival benefit from repeat resection, differentiation of the recurrent type is of great importance. Our previous study revealed that the recurrence-free time was the most important differentiating factor between the IM and MO patients, and a recurrence-free period of 18 months was the best cut-off time to differentiate between IM and MO (Figure 4).

Salvage liver transplantation (SLT) is another treatment of choice for recurrent HCC. It has been widely accepted that SLT should be used for patients who fulfill the Milan criteria. A study based on analysis of the European Liver Transplant Registry indicated that HCC recurrence in patients who previously underwent liver resection would often present with multiple tumor nodules, and only 25% of patients with recurrent tumors fulfilled the Milan criteria (Mergental and Porte, 2010). Studies also indicated that liver transplant was only feasible in 23% of patients with recurrent HCC (Adam et al., 2003). Our clinical data show that in patients with recurrent HCC beyond the Milan criteria, the 3-year recurrence rate and overall survival rate after SLT are 86.1%, and 40.6%, respectively (Liang et al., 2014). Our data suggest that SLT should not be recommended to patients with recurrent HCC beyond the Milan criteria.

LIVER TRANSPLANTATION

According to a 2011 estimate, about 300,000 people in China develop end-stage liver disease each year. The only treatment available to these patients used to be whole-liver transplantation. However, many patients died due to a se-

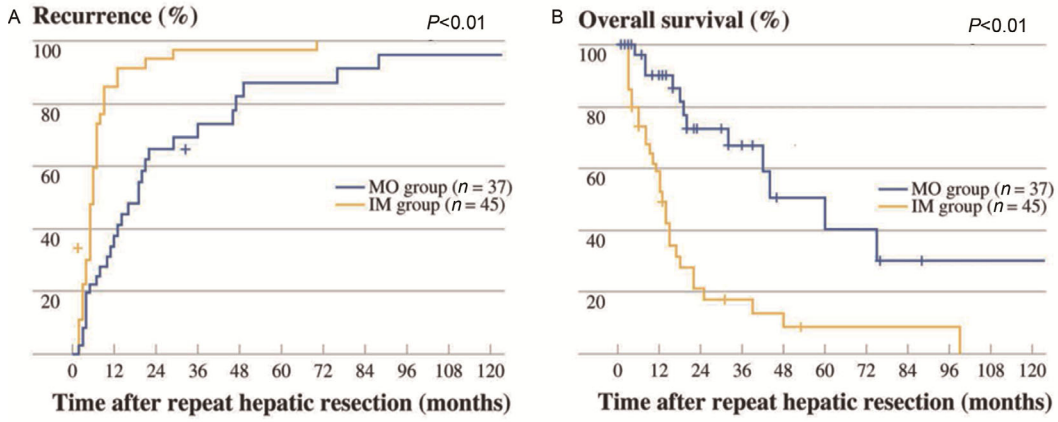

Figure 4 (Color online) The recurrence curves (A) and overall survival curves (B) of the multicentric occurrence (MO) group and intrahepatic metastasis (IM) group (Huang et al., 2012).

vere shortage of organ donors.

To address the shortage, we began to develop living-donor liver transplantation, which involves surgically removing a portion of the liver from a living donor. Because this technique does not require replacing the entire liver, one donor liver can be shared between two patients, thus mitigating the shortage of donor organs.

Auxiliary liver transplantation can be used to treat some liver diseases but the success rate of these operations was low—about 10%—in the early 1980s. The primary reason for failure was that the limited space in the patient's abdomen for the donor liver required the donor liver to be placed in an abnormal position, which was detrimental to the reconstruction of blood circulation. To address this problem, in 1983 we developed the first animal model for studying auxiliary partial orthotopic liver transplantation (Figure 5). The procedure involved cutting out 40% of the right liver of the canine model and transplanting a partial liver graft (37% of the total donor liver) onto the recipient liver. The procedure solved the problem of space and enabled blood circulation to be reconstructed effectively. Our successful experiments and clinical applications in 13 cases demonstrated that the procedure was safe, effective and feasible.

HILAR CHOLANGIOCARCINOMA

Major or minor hepatic resection

Hilar cholangiocarcinoma is the most common form of cancer to affect the biliary tract. Only a very few patients with unresectable, indolent and slow-growing hilar cholangiocarcinoma can achieve long-term survival (Ruys et al., 2012). The prognosis of most patients with unresectable tumor is poor, with a median survival of less than 1 year, because of the vital position of the tumor. The treatment for hilar cholangiocarcinoma is challenging. Surgical treatment offers the only possibility of cure, and it requires removal of all tumor tissues with adequate resection margins.

Common strategies for surgically treating hilar cholangiocarcinoma are hemihepatectomy with caudate lobectomy or extended hemihepatectomy, a procedure that involves 60%–80% resection of the liver. However, extensive resection of the liver inevitably results in high rates of postoperative complications and mortality. There are still controversies on the optimal extent of hepatic resection to achieve a high percentage of R0 resection for hilar cholangiocarcinoma.

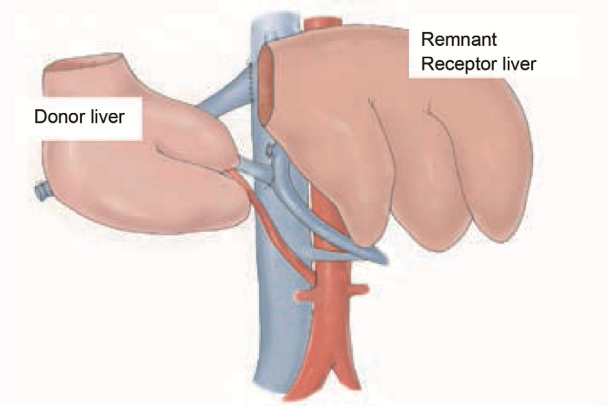

Figure 5 (Color online) In 1983, Chen developed the first canine model of auxiliary partial orthotopic liver transplantation.

Combined major liver resection represents an aggressive surgical approach to remove a large volume of hepatic parenchyma, including the use of right trisectionectomy, right hemihepatectomy, left trisectionectomy, or left hemihepatectomy. This approach has widely been advocated as a prime choice of surgical treatment for hilar cholangiocarcinoma, especially in patients with advanced tumors (Witzigmann et al., 2006). Combined major liver resection has the advantage of increasing surgical curability by obtaining wide and negative surgical resection margins (Nagino et al., 2006). In addition, hemihepatectomy/trisectionectomy is technically feasible and can be performed by many surgeons. The major drawback of combined major liver resection is the small post-operative liver remnant, which is associated with high surgical morbidities and mortalities (Dinant et al., 2006). Thus, the increase in resectability rate can be offset by the increase in postoperative mortality after major liver resection.

A decrease in morbidity and mortality after liver resection is the key strategy for improving the results of surgical treatment of HC. Minor liver resection (three or fewer segments according to the Couinaud nomenclature) may be one way to resolve the problem. For early (T)-stage HC, minor resection of segments I, IVb and V has been performed to excise the tumor with adequate margins, termed "central liver resection".

We noticed that around 90% of the resected liver tissue was normal tissue, unaffected by the malignant tumor. We hypothesized that it would be possible to reduce the amount of resected liver tissue while ensuring the removal of the entire area by the tumor.

Through pathological studies in 90 cases, we observed that hilar cholangiocarcinomas are typically 1–3 centimeters in diameter, often arising at the confluence of the left and right hepatic ducts and spreading only 2–8 millimeters along the bile duct wall. This finding indicated that resection of only about 20% of the liver would be necessary to treat the disease. Through clinical studies, we discovered that small volume liver resection significantly lowered post-operative rates of complications and mortality and we obtained similar long-term treatment outcomes compared to more extensive liver resection. In this prospective clinical study, 138 patients underwent resection with curative intent. Minor hepatectomy was performed in 93 patients with Bismuth-Corlette type I, II, or III HC without hepatic arterial or portal venous invasion, and major hepatectomy in 45 patients with type III HC with hepatic arterial or portal venous invasion, or type IV HC. Actuarial 1-, 3-, and 5-year sur-

vival rates were 87%, 54%, and 34%, respectively, in the minor liver resection group, and 80%, 42% and 27% for major resection (P=0.300) (Figure 6). Major liver resection was associated with a higher operative morbidity rate than minor resection. Therefore, minor liver resection for HC, selected by predetermined criteria, had good results. Major liver resection should be reserved for Bismuth-Corlette type III HC with vascular invasion or type IV HC.

In 2014, the Liver Surgery Group of the Surgical Branch of the Chinese Medical Association lead by Dr. Chen drafted a consensus for the diagnosis and treatment of cholangiocarcinoma (Chinese Chapter of International Hepato-Pancreato-Biliary et al., 2014), including HC. This consensus lays down a foundation for establishing a guideline on diagnosis and treatment of cholangiocarcinoma in China.

Inserting biliary-enteric anastomosis technique

Another common challenge in hepatobiliary surgery is related to the surgical procedure known as biliary-enteric anastomosis performed on small bile ducts. The main difficulty in minor liver resection for HC is biliary tract reconstruction, because as many as 8–13 bile duct openings are left in the transection plane of the liver. In this situation, biliary tract reconstruction cannot be completed with traditional methods. Following numerous experiments, we established an inserting biliary-enteric anastomosis technique and applied it to auxiliary partial orthotopic liver transplantation and the reconstruction of the biliary tract when bile ducts are accidently injured during a prior biliary surgery (Yang et al., 2015). We later improved this technique by performing biliary-enteric anastomosis without stitching the anterior wall of the bile ducts—a useful modification for complex biliary operations, especially for the reconstruction of the biliary tract after central hepatectomy during hilar cholangiocarcinoma treatment.

In the classical hepaticojejunostomy, the hepatic duct was anastomosed to the jejunum by using a mucosa-to-mucosa anastomosis. The operation is difficult for small bile ducts in the small operative space. The difficulty of the operation increases with decreases in the diameter of the bile ducts. In new intrahepatic cholangiojejunostomy, the posterior wall of the bile ducts is sutured to the posterior wall of the intestine, and then, the anterior wall of the intestine is sutured to the liver transection plane. The operative space is large and vision is clear, making the operation relatively simple (Figure 7).

The new intrahepatic cholangiojejunostomy solves the problem of reconstruction of multiple small bile ductal openings after hepatobiliary resection. The procedure is safe, simple, and convenient, and it does not require placement of a stent across the anastomosis. After the operation, the anastomotic stoma heals with low incidences of postoperative bile leak, excessive anastomotic stenosis, and symptomatic postoperative obstructive jaundice and cholangitis (Yang et al., 2015).

PANCREATIC DISEASE

Invaginated pancreaticojejunostomy with transpancreatic U-sutures

Pancreatoduodenectomy (PD) is the most effective therapy for treating malignant tumors at the head of the pancreas, the lower common bile duct, and the duodenum of the small intestine. A critical procedure in this operation is known as pancreaticojejunostomy (PJ), which currently involves time-consuming and complex stitching. The procedure is associated with a high incidence of postoperative pancreatic fistula (POPF), which may lead to postoperative mortality. The POPF rate ranges from 5% to 40%, even in specialized centers, depending on the definitions used (Cameron et al., 2006). The POPF rate does not seem to have declined in the same way as the mortality rate has over the last few decades (Neoptolemos et al., 1997). Hemorrhage and sepsis are the most frequent sequels of POPF, both of which contribute to mortality (20%–40%) as well as to prolonged hospitaliza-

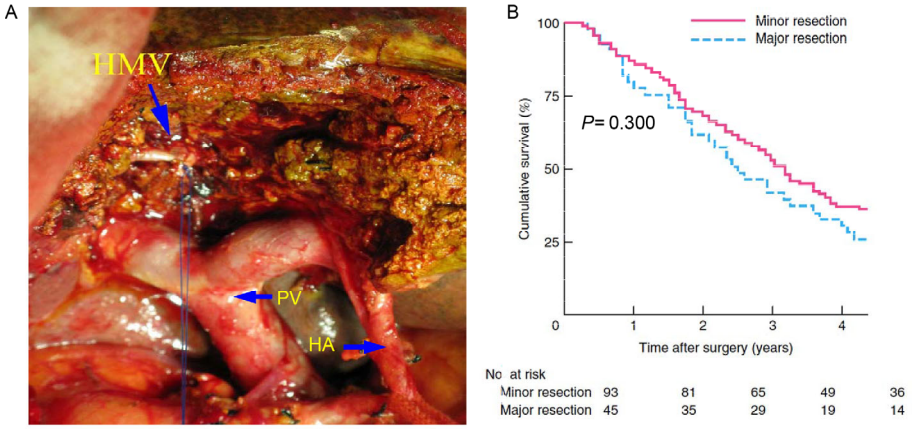

Figure 6 (Color online) Minor liver resection for hilar cholangiocarcinoma. A, Resection plane after minor liver resection for HC. B, Kaplan-Meier overall survival curves for patients undergoing minor and major liver resection for hilar cholangiocarcinoma. P=0.300 (Chen et al., 2009).

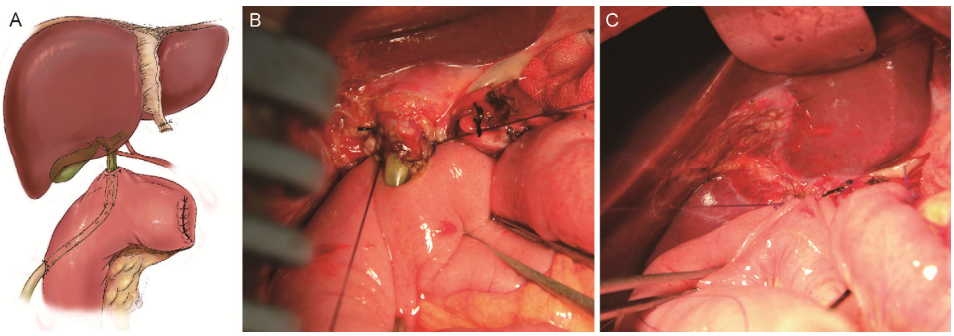

Figure 7 (Color online) Diagram and intraoperative photograph of the inserting biliary-enteric anastomosis. A, Diagram of the inserting biliary-enteric anastomosis. B, The posterior wall of the jejunum has been anastomosed to the posterior biliary ductal wall. C, Anterior anastomosis has been completed by intermittent U suture between the jejunum and the edge of the liver transection plane.

tion and increased hospital cost (Bottger and Junginger, 1999; Trede and Schwall, 1988).

POPF remains a major cause of postoperative morbidity, and it contributes significantly to mortality (Lai et al., 2009). In an attempt to prevent postoperative complications, especially POPF, many refinements of procedures have been proposed. In the past 30 years, over 50 types of pancreatic and digestive tract reconstruction techniques have been reported. The increase in number of techniques of pancreatic and digestive tract reconstruction reflects the pancreatic surgeons' continuous efforts to reduce complications of pancreatic surgery, aiming to refine pancreatic and digestive tract reconstruction so as to develop a better anastomotic method to reduce complications after PD. On the other hand, the emergence of a variety of surgical methods indicates that there is currently no perfect method. The best pancreatic anastomosis technique after PD is still under debate.

Invaginated pancreaticojejunostomy (IPJ) is performed by invagination of the pancreatic stump into the intestine in either an end-to-end or an end-to-side manner. For ease of performance, identification of the main pancreatic duct is not required, and in accordance with the physiological structure of the digestive tract, IPJ has been considered as the conventional and classic anastomosis method from the origin of the PD and is the most common type of PJ used nowadays. The incidence of postoperative complications has also been regarded as standard for evaluation of different techniques.

As reported in many publications, the POPF rate varies greatly in different reports in patients after IPJ because of variations in definitions used. In a review by Bassi et al., the incidence ranged between 9.9% and 28.5% and the different definitions used for pancreatic leakage resulted in highly significant differences across studies (Bassi et al., 2005). Other complications often occur after the onset of POPF. Post-operative bleeding due to erosion of peripancreatic vessels by extravasated pancreatic juice has been described in 2%–8% of cases (Rumstadt et al., 1998). The morbidity rate increased from 6% to 26% when POPF manifested (Zealley et al., 2006).

In this context, we established a procedure described as invaginated pancreaticojejunostomy with transpancreatic U-sutures, which requires only two-to-four stitches and saves significant time with reliable effects (Figure 8). The real magic of the technique comes from the "automatic" insertion of the pancreatic stump into the intestinal lumen simply by pulling the U-suture stitches—a process that cannot be achieved using any other pancreaticojejunostomy technique. The innovation has proven to be a breakthrough for pancreatoduodenectomy and pancreaticojejunostomy.

In 1995, our group established the Chen's U-stitch approach, which was a new technique of end-to-end invaginated pancreaticojejunostomy with transpancreatic transverse U-sutures after PD, and the preliminary results were quite encouraging at that time (Chen et al., 2009). In 88 patients who underwent a transpancreatic U-sutures IPJ PD, only 2 patients (2.2%) developed a grade A POPF.

Over the past 10 years, this technique has been used in 264 patients who underwent pancreaticojejunostomy after PD, and excellent perioperative outcomes have been demonstrated. By 2014, a new clinical study including 264 patients had been completed to further evaluate the clinical efficacy of this surgical approach (Chen et al., 2014). Among the patients who underwent transpancreatic U-sutures IPJ PD, postoperative morbidity was 22.3% (59/264) and mortality was 0% (0/264). The POPF rate was 3.4% (9/264) for Grade A, 0.8% (2/264) for Grade B and 0% (0/264) for Grade C. Therefore, the fistula-related morbidity and mortality was largely avoided by using this new surgical technique.

The pancreas is extremely prone to injury from a pancreatic fistula. Experience has shown that if there is even a small pinhole on the pancreas, a pancreatic fistula will occur. This is one of the main reasons for pancreatic fistula development after the traditional methods of pancreaticojejunostomy. The more the stitches used or pinholes created during a PD procedure, the higher the probability of developing a pancreatic fistula. The low incidence of POPF following pancreaticojejunostomy with transpancreatic

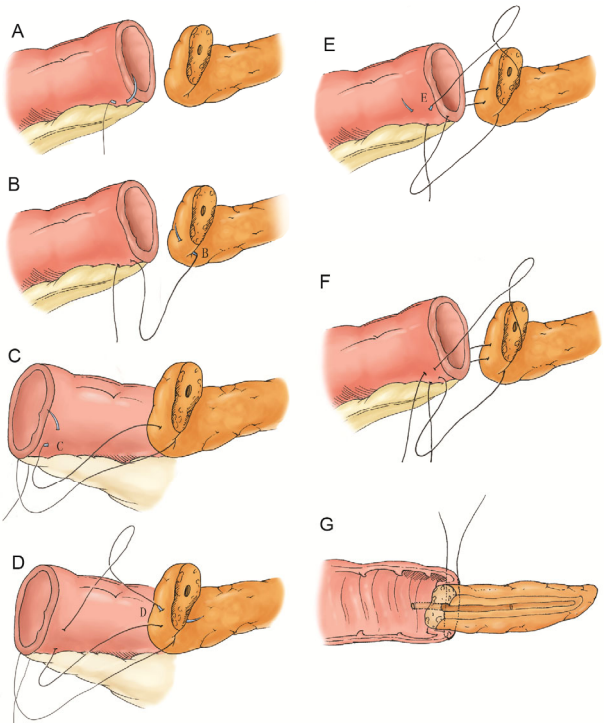

Figure 8 (Color online) Invaginated pancreaticojejunostomy with transpancreatic U-sutures technique. A, Expose the anterior wall of the jejunal loop. At about 1.5 cm from the bowel resection margin near the mesentery, insert the needle from outside. Then, stitch the needle from inside to outside at about 0.5 cm from the bowel resection margin. B, Steer the needle to the pancreas. At about 1.5 cm from the stump of the lower edge of the pancreas, insert the needle from the ventral pancreas (front) and run through the pancreatic parenchyma to the dorsal pancreas (back). C, Steer the needle to the posterior wall of the jejunal loop. Insert the needle from outside at about 1.5 cm from the bowel resection margin and stitch through to the inside. Stitch horizontally from inside and exit the needle from about 1.0 cm of the insert pinhole. D, Steer the needle to the dorsal pancreas (back) of the lower edge. Insert the needle at about 0.8–1.0 cm of the first pinhole, run through the pancreatic parenchyma, and exit the needle from the ventral pancreas (front). E, Steer the needle to the anterior wall of the jejunal loop. Insert the needle at about 0.5 cm from bowel resection margin from the outside to the inside, and then exit the needle from the inside to the outside at 1.5 cm of the bowel resection margin. F–G, The first horizontal U shape Varus stitching is completed.

transverse U-sutures described here is ascribed to the following four reasons: (i) it requires less dissection of the pancreatic stump, thus reducing the risk of pancreatic injury; (ii) there are fewer stitches (two to four U-sutures) and pinholes made within the pancreas; (iii) the full-thickness of the anterior and posterior walls of the jejunum loop presses on the pinholes of the pancreas after ligating the U-sutures, thus preventing the exudation of pancreatic juice from the pinholes and the occurrence of pancreatic fistula; and (iv) the pancreatic stump can be firmly invaginated into the jejunum loop through transpancreatic transverse U-sutures.

CONCLUSION

In the past 30 years, great progress has been made in the treatment of HPB diseases owing to improved peri-operative management, better patient evaluation, improved surgical technique, and better understanding of anatomy.

Most of our patients are found to have large HCC tumors or intermediate/advanced HCC at their first medical consultation. Surgical resection remains the main treatment approach for large HCC tumors and intermediate/advanced HCC, and recent improvements in surgical techniques and peri-operative care have enhanced the feasibility and safety of liver resection, leading to favorable long-term outcomes in selected patients. However, there is no universal consensus on the management of large HCC tumors and intermediate/advanced HCC in clinical practice. At Tongji Hospital, we have adopted a multidisciplinary approach to enhance long-term survival rates and to improve the quality of life of patients with HCC.

The prognosis of malignancies in the pancreato-biliary system remains poor, and post-operative complications are relatively high. At Tongji Hospital, we carefully selected patients with pancreato-biliary tumors for surgical treatment, and innovated biliary-enteric anastomosis and pancreas-enteric anastomosis to reduce complications. Further studies will focus on therapeutic strategies, such as combined treatments, to reduce post-operative complications and improve long-term survival.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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