PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

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Editorial

Progress in research of liver surgery in China

Meng Chao Wu and Feng Shen

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INTRODUCTION

Liver surgery, was started in the late 1950s in China and has developed rapidly in the past 40 years[1]. The study on the diagnosis and treatment of primary liver cancer in China underwent four stages: ① In the 1950s, the anatomical study of the liver lay a solid foundation for liver resection[2]. ② In the 1960s and 1970s, studies mainly focused on the detecting methods of AFP and other tumor markers, clinical and pathologic characterion of small liver cancer and epidemiology of liver cancer. ③ In the 1980s, imaging diagnostic techniques, such as CT, MRI, DSA, Doppler ultrasonography, etc., and new therapeutics[3], such as hepatic artery chemo-embolization, percutaneous intra-tumoral ethanol injection, hepatic artery ligation with targeted chemotherapy[4], and some new concepts such as radical regional resection, re-operation of the recurrent liver cancer, two-stage resection, the combined surgical management of liver cancer complicated with hepatic duct thrombus, splenomegaly and portal hypertension were introduced. These comprehensive treatment further improved the liver cancer surgery. ④ In the 1990s, attention was mainly focused on the biotherapy and liver transplantation. The progress in the diagnosis and treatment of primary liver cancer in recent years are summarized as follows.

EARLY DETECTION OF LIVER CANCER

The methods for early detection of liver cancer include: ① People aged more than 35 years, with a history of hepatitis, HBV or HCV infection, cirrhosis or chronic hepatitis, should be taken as a high risk population. Periodical monitoring of this population is the key step to detect early liver cancers; ② AFP and B-US screening is, at present, the most sensitive, convenient and economical method for detecting early liver cancers; ③ for patients with low level AFP, the AFP variant detection is helpful[5]. As to the patients with negative AFP, other liver tumor markers can also be used; ④ combined with CT, MRI, CTA or DSA, B-type ultrasonography is useful in the early diagnosis and localization of liver cancer; and ⑤ fine needle puncture for cytologic study and ethanol injection under ultrasonography is also helpful.

TREATMENT OF LIVER CANCER

At present, hepatectomy remains the treatment of choice for primary liver cancer [6]. The efficacy of surgical intervention has been raised rapidly and significantly since 1978[7]. The main reasons are as follows: ① the improvement of diagnostic methods for early cancer, ② renewal of surgical concepts; ③ improvement of surgical techniques and perioperative management[8], and ④ the development of comprehensive therapy postoperatively. The pathological data from our group showed that 86. 5% liver cancers were concomitant with cirrhosis or chronic hepatitis. The regular or extended hepatectomy might lead to severe decompensation of liver function. Therefore, the modality of liver resection drifted from an extended one to an irregular radical local resection[9]. With presence of chronic hepatitis or cirrhosis, the radical local resection modality not only increases the resectability, but also significantly decreases the surgical mortality rate and attains the same long-term effect as the extended resection, or even better. The patients used to be given con servative therapy when one or more complications occurred such as jaundice, severe portal hypertension and esophageal varices with or without hemorrhage. With the accumulation of clinical experience, obstructive jaundice resulting from oppression of hepatic hilus or cancerous thrombi invading the biliary duct could be treated with hepatectomy or the removal of the biliary duct thrombi if hepatocellular jaundice and other contraindications could be excluded[10]. Usually, the jaundice disappeared gradually after operation. In the patients with splenomegaly, hypersplenism and esophageal varices with or without hemorrhage, the hepatectomy can also be performed together with splenectomy plus ligation of varices or with splenorenal shunt. In the past, the comprehensive therapy was mainly used for advanced liver cancers

Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai 200438, China
Prof. Meng Chao Wu, graduated from Tongji Medical College in 1949, Academician of Chinese Academy of Sciences, specialized in hepatic surgery, having more than 200 papers published.
Correspondence to: Prof. Meng Chao Wu, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai 200438, China
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that were unresectable[11]. But now, this concept has been extended and includes ① the pre- and post-operative comprehensive therapy for resectable liver cancer to prevent recurrence; ② palliative removal of irresectable tumors followed by anti-cancer therapy to shrink the tumor mass and prolong the tumor bearing survival period; and ③ comprehensive therapy for temporarily non-eligible surgical patients, with the hope of performing two-stage resection and long-term tumor bearing survival period.

Comprehensive therapy includes surgical and non-surgical treatment[12] , the former including hepatectomy, hepatic artery ligation (HAL), operative hepatic artery embolization (OHAE), drug delivery system (DDS), intraoperative ethanol injection, microwave consolidation[13], laser gasifi cation, freezing, etc. and the latter including transcatheter arterial chemo-embolization (TACE)[14], B-US directed percutaneous ethanol injection (PEI) or other drugs[15], radioisotopes and bio-agents, biotherapy, radiotherapy and traditional Chinese medicine.

Rational comprehensive therapy with multimodality is superior to a single method in terms of effectiveness[16]. The tetralogy of comprehensive surgical therapy, which is the combination of HAL, OHAE, DDS and radiotherapy performed in 603 advanced liver cancers in our hospital, showed that the rates of two-stage resection and 1, 3 and 5-year survival rates were significantly higher than that of a single procedure (HAL or OHAE). The incidence of recurrence was only 7.4% in the 27 cases treated with comprehensive immunochemotherapy (cytokines plus low-dose chemotherapy) after resection, whereas in the control groups, it was 32%. In 86 operated cases, DDS chemotherapy was performed and the total incidence of one-year recurrence was 34.9%, while in hepatic artery, portal vein and hepatic artery combined with portal vein groups were 33.3%, 34.6% and 23.6%, respectively. Non-surgical comprehensive therapy was eligible for all patients with unresectable liver cancer, the TACE and intra-tumoral drug injection being most popular. In a series of 8000 TACE cases, the 3-year survival rate was 13.9%. The drugs we used in the B-US directed local drug injection were absolute ethanol, ^{32}P radioisotope, OK432, TNF-alpha and IL-2. The 2-year survival rate in 700 patients receiving PEI was 80.0%, with a total of 3000 injections given. In another group of 113 patients receiving TACE in combination with PEI, the tumors shrank in most patients (91.2%) in varying degrees, and the total 2-year survival rate was 81.6%. Among them, 11 out of 71 patients with tremendons, solitory tumor received two-stage resection after the tumor shrinkage and the two-stage resection rate was 15.49%.

Comprehensive therapy is not simply a random combination of various methods. The design of the protocol should be individualized and case-specific. The regimen of the comprehensive therapy is multiple in medical literature. We propose two principles: ① The two methods used should be complimentary; and ② no contradiction in their effects and the side effects should not be additive. At the same time, attention should be paid to the toxic effect of each method and not to pose damage to the liver function. Besides, special emphasis should be laid on the effectiveness and use of traditional Chinese medicine in comprehensive therapy.

In 1978, we reported that a two-stage resection of a large-sized liver cancer shrunk after HAL procedure. Since then, this procedure has became a promising modality for unresectable large liver cancers. At present, the comprehensive surgical methods for massive liver cancer shrinkage comprise HAL, HOHAE and DDS, and non-surgical procedures, such as TACE, PEI, target therapy and radiotherapy. A rational combination of these methods enables some unresectable tumors to become resectable if they were sequencially employed. From 1974 to 1994, 649 patients received this therapy and 73 of them had their tumors resected with a resectability rate of 11.1% without operative death. The 5-year survival rate was 61.5% postoperatively, the longest survival being 17 years. The pathological data in this group showed that there were still some viable cancer cells remained although the tumor had shrunk due to the comprehensive therapy, it was still essential to remove the tumor remnants. At present, two-stage resectability rates are still very low, because no generally accepted criteria for tumor resectability. We propose that the two-stage resection is indicated only for those really unresectable, otherwise, the one-stage removal is of first choice; rational employment of comprehensive therapy is crucial for tumor shrinkage; and the unresectable liver cancers should be subjected to non-surgical comprehensive therapy, such as TACE, PEI and guided chemoimmunotherapy as the first choice.

BASIC RESEARCH IN LIVER CANCER

In the 1960s, the study of the liver cancer focused on the basic surgical study, including the anatomy of the liver, the postoperative hepatic metabolism and the effects of hilar occlusion on the hemodynamics and the metabolism of the liver. In that period, epidemiological study of the HBV and aflatoxin on liver cancer were completed in small samples. The first hepatoma cell line in the world was established, and the induced liver cancer models in rats were set up in many institutes. However, the study only stayed at the basic clinical level.

In the 1970s, much research work was concentrated on the relationship of AFP and the liver cancer. Various assays for AFP were set up and their sensitivity and specificity were tested. The

clinical and pathological characteristics of small liver cancer were documented. Contaminated food, water and HBV were shown as the main factors promoting liver cancer in high incidence areas as shown by epidemiological study in China. The first-line prophylactic strategy, that is, water control, fungi prophylaxis and hepatitis control was established. For the first time, liver cancer study in China appeared to have its own characteristics.

In the 1980s, liver cancer study in China reached cellular and molecular levels. The relationship between HBV and liver cancer was corroborated at the molecular level[17]. The relationship between the DNA content of the liver cancer tissues and their biological features was documented with pathological study in liver cancer at cellular and molecular levels. Gene spectrum of liver cancer was found. HBV-DNA integration was verified as the activation factor of some oncogenes. The immunological status of liver cancer hosts and its relationship with tumor were studied[18]. The biological significance of the agglutinin, sugar, gangliosides, serum enzymes[19] and protein to liver cancer and also the interventional methods were observed. Monoclonal antibodies specifically targeting the membrane antigens had been generated, and their localization *in vivo* and targeted treatment were studied[20]. A lot of work was done on the serum tumor markers.

In the 1990s, a series of oncogenes and tumor suppressive genes were found by cellular, molecular and gene-manipulating methods. The relationship of HBV, HCV, aflatoxin and other cancer-inducing factors and the mutation of oncogenes and tumor suppressive genes, and their mechanisms were elucidated. The role of the genes, such as *p*16, *p*53 and *nm*23-H1 and the enzymes and adhesiv e molecules such as metaloproteinase, CD44, ICAM-1, integrin in metastasis and recurrence of liver cancer were verified. The clonogenicity of the liver cancer was studied with DNA, oncogene and tumor suppressive gene. The mechanisms of the cell cycle control, apoptosis, senescence evading and the escape of the immunologic surveillance of liver cancer cells were studied. And in the related study of the cellular signal transduction in these processes, the negative control genes on the liver cancer growth were found. The liver cancer-related genes were found with screening of a large amount of liver cancer genome, and even in some genes, their functions and chromosome localization were also elucidated[21]. In immuno logical study, many kinds of tumor vaccines have been produced. Many researches in gene therapy, induction-differentiation, prophylactic control of neoangiogenesis of liver cancer are being carried out, reaching world advanced level.

LIVER TRANSPLANTATION

It is controversial about the indications of liver transplantation in liver cancer[22]. In massive liver cancers, recurrence after transplantation is unavoidable due to vascular invasion and distal metastasis as well as the use of immunosuppressive agents[23]. On the contrary, the therapeutic effects of liver transplantation on small liver cancers complicated with severe cirrhosis are corroborated. Comparing the therapeutic effects of hepatectomy and liver transplantation, Bismuth concluded that the 3-year survival rates were almost the same, while the tumor-free 3-year survival rate was higher by liver transplantation than by hepatectomy. As to the small liver cancer (mononodular or binodular, with a diameter less than 3cm), the results of liver transplantation were even better. Selby *et al* showed that the total 5-year survival rate in 105 cases of unresectable liver cancer of different stages that received liver transplantation was 36%, of whom the 5-year survival rate from stage one to three was 52.1%, while in stage four, it declined to 11%. They concluded that liver transplantation was fit for liver cancer in early stage ($\leqslant$2cm, no vascular invasion and no distal metastasis). Although we do not have enough data, liver transplantation should not be regarded as a routine therapeutic method because of high incidence of liver cancer, liver donation shortage and high cost in our country.

PERSPECTIVE

Further progress of liver cancer research in our country depends on the progress in multiple factors, such as further studies of the individual and circumstantial factors on the genesis of liver cancer and its mechanisms, the mechanisms of metastasis and recurrence after hepatectomy[24], the recognition of liver cancer-specific antigens and genes and their signaling pathways, in order to find out the measures intervening the genesis and growth of the tumor. Attention should be paid to the precancerous lesions of liver. The definition of precancerous lesion at molecular level and the study on blockage of its tran sformation will enhance the efficacy of liver cancer treatment. In clinical practice we should stick to the principles of early diagnosis and early management, and the surgical treatment is still the treatment of choice. Pre- and post-operative TACE and other comprehensive treatment modalities should be studied to improve the tumor-free survival. The regional therapy of liver cancer, such as the intra-tumoral injection treatment and regional treatment should be generated with new techniques and new approach. The radiotherapy, biological therapy and traditional Chinese medicine are hopeful. The regimens we employ now are to be combined to fit different cases. Shrinkage of the massive liver cancer into small one and anti-recurrence therapy are the main goals of our practice. The liver transplantation should be actively applied for early liver cancer.

Due to the large number of people infected with HBV or HCV as the background of liver cancer, the liver cancer is still a major life threatening disease among Chinese people, therefore, surgical treatment should be further strengthened.

REFERENCES

1 Tang ZY. Advances in clinical research of hepatocellular carcinoma in China. *Huaren Xiaohua Zazhi*, 1998;6:1013-1016
2 Liver disease study group of second military medical college. Intrahepatic anatomy of normal people in China. *Zhonghua Waike Zazhi*, 1962;2:97-103
3 Yang CH, Liu YX, Feng YQ. Double embolization for the treatment of advanced liver cancer via hepatic artery and portal vein. *Zhonghua Waike Zazhi*, 1996;34:575
4 Tang ZY, Liu KD, Fan Z, Lu JZ, Zhang YJ, Hou Z, Bao YM, Zhou D, Tang WY, Xia XL, Yang R, Yu ZY, Lin ZY, Ma ZC, Zhou XD, Yu YQ, Yang BH, Zhao HY, Yuan AN, Zhou YG. Targeting therapy of hepatocellular carcinoma: experimental and clinical studies. *Zhongliu*, 1990;10:241-245
5 Tu ZX, Wu MC, Cui ZF, Hu HK. The value of AFP variant for the early detection of primary hepatocellular carcinoma. *Zhonghua Neike Zazhi*, 1986;25:272-275
6 Wu MC, Chen H, Zhang XH, Yao XP, Yang JM. 18-year experience of hepatectomy for primary liver cancer. *Jiefangjun Yixue Zazhi*, 1979;4:85-88
7 Wu MC, Chen H, Yao XP, Yang JM, Yang GS, Shen F. Surgical treatment of primary liver cancer. *Zhonghua Waike Zazhi*, 1996;34:707-710
8 Wu MC, Zhang XH, Hu HK, Chen H. Middle lobe resection for the treatment of middle lobe carcinoma. *Jiefangjun Yixue Zazhi*, 1963; 2:363-368
9 Chen XP, Gao YM, Wu ZD, Qiu FZ. 30 cases of hepatic segmentectomy. *Shiyong Waike Zazhi*, 1989;9:261-262
10 Chen JQ, Zhu CS, Li QR, Qin SM, Shen H, Wang LJ, Liu T, Ding SC, Wei YZ. Extrohepatic obstructive jaundice caused by the hepatocellular cancerous thrombi. *Zhonghua Waike Zazhi*, 1996;34:18
11 Zhang XH, Wu MC, Yao XP, Jiang ZX. Operative hepatic artery embolization for the treatment of primary liver cancer 16 cases report. *Zhongliu*, 1983;3:9-12
12 Huang JF, Wang WS, Liang LS, Lue MD. Treatment of irresectable hepatocellular carcinoma with repeated transient dearterialization. *Zhonghua Waike Zazhi*, 1996;34:522-525
13 Dong BW, Liang P, Yu XL, Zeng XQ, Wang PJ, Wang XD, Su L, Ni XX, Xu Y. US-guided microwave in the treatment of liver cancer: experimental study and preliminary clinical application. *Zhonghua Yixue Zazhi*, 1996;76:87-91
14 Jia YC, Tian JM, Wang ZT, Chen D, Ye H,Liu Q, Yang JJ, Sun F, Lin L, Lu JP, Wang F, Cheng HY. A retrospective review on interventional treatment of 10000 cases of liver cancer. *Huaren Xiaohua Zazhi*, 1998;6:2-3
15 Dong BW. General principles for B-US directed liver cancer intervention therapy. *Zhonghua Yixue Zazhi*, 1996;76:83-84
16 Zhou XD, Tang ZY, Yu YQ, Yang BH, Ma ZC, Lu JZ, Lin ZY, Ye SL, Wu ZQ. Long-term results of multimodality treatment in patients with primary liver cancer. *Zhonghua Waike Zazhi*, 1996;34:518-521
17 Chen YQ, Jiang HQ, Gu JR, Cao YZ, Liao JC. The status of HBV DNA in human primary liver cancer and peri-tumor tissues and its significance. *Shanghai Yixue*, 1988;11:63-67
18 Shen F, Wang H, Xie TP, Shi LH, Qian WZ, Liu XY, Wu MC, Guo YJ. Experimental and clinical research of cytolytic T lymphocytes specific for hepatocellular carcinoma. *Zhonghua Waike Zazhi*, 1997;35:95-99
19 Zhang SM, Wu MC, Chen H, Tu ZX, Cui ZF, Yu ZQ, Huang LB, Ye ZX, Qian BH, Zhang XZ. The value of glycotidase spectrum in the diagnosis of hepatocellular carcinoma. *Zhonghua Zhongliu Zazhi*, 1992;14:143-145
20 Wang Q, Chen ZN, Wang WL, Liu ZG, Wang WX, Liu CG, Xu LQ, Qiu K. Anti-tumor effects of bispecific monoclonal antibody targeted human monocytes-macrophages on hepatoma cells. *Zhonghua Yixue Zazhi*, 1996;76:96-99
21 Li BA, Wang HY, Chen ZJ, Wu MC. Expression of signal-regulatory protein α(SIRPα) in hepatocellular carcinoma. *Zhonghua Zhongliu Zazhi*, 1998;20:345-347
22 Lin YZ, Tang BY, Hong HQ, Yin HR, Zhu SL, Xue YS, Bian GL, Fu PB, Dong FZ, Jiang SH. Allogenic orthotopic liver transplantation. *Zhonghua Qiguan Yizhi Zazhi*, 1980;1:21-25
23 Wu MC, Zhang XH, Chen H, Yao XP, Wu BW, Yang JM. Allogenic orthotopic liver transplantation-3 case report. *Zhonghua Qiguan Yizhi Zazhi*, 1984;5:121-123
24 Liu KD, Tang ZY, Yu YQ, Zhou XD, Ma ZC, Lu JZ, Lin ZY, Zhang BH. Factors influencing the liver cancer recurrence and their significance. *Zhonghua Yixue Zazhi*, 1996;76:617

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