Clinical research advances in primary liver cancer

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Primary liver cancer (PLC) is one of the most common cancers in China. According to the statistics of our country, primary liver cancer claims 20-40 lives per100 000 people annually, with 19.98 per100 000 in cities and 23.59 per 100 000 in rural areas, ranking as the second and the first leading cause of cancer death respectively. Of all the newly enrolled cases in the world each year, 45% are found in the mainland of China. In the southeast areas of high incidence, the situation is even worse that the tumor tends to occur in a younger age group.

In China, the research in the diagnosis and treatment of primary liver cancer has undergone four stages: ① in the 1950s, the anatomical study of the liver lay a solid foundation for liver resection. ② In the 1960s and 1970s, as the detection of AFP and other liver cancer markers were widely used, the ability of early diagnosis was greatly improved with a better therapeutic effect. ③ In the 1980s, the introduction of some new techniques, such as CT, MRI, DSA, Doppler ultrasonography, etc., some new methods, such as hepatic artery chemoembolization (TACE), percutaneous intra-tumor ethanol injection (PEI), hepatic artery ligation (HAL) plus catheterized chemotherapy and target therapy, and some new concepts, such as curative local resection, reoperation of the recurrent liver cancer, two-stage resection, the combined surgical management of liver cancer complicated with biliary duct thrombi, splenomegaly, portal hypertension and comprehensive treatment further enhanced the development of liver cancer surgery. ④ In the 1990s, the concept of comprehensive therapy focusing mainly on surgery, the biotherapy strategy based on the rapidly developing molecular biology research and the study of liver transplantation for liver cancer are paid close attention.

The progress of diagnosis and treatment of primary liver cancer in recent years can be summarized as follows.

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EARLY DETECTION OF LIVER CANCER AND THE CHANGE OF THE CONCEPT OF SMALL LIVER CANCER

The methods for early detection of liver cancer include: ① men aged more than 35 years, with a history of hepatitis, and positive HBV or HCV, associated with cirrhosis or chronic hepatitis, should be recognized as a high risk population. Periodical monitoring of this population is a key step to find early liver cancers. ② AFP and B-US screening are, at present, the most sensitive, convenient and economical methods for detecting early liver cancers. ③ For the patients with low level AFP, AFP variant detection is helpful. As to the patients with negative AFP, other liver cancer markers can be used for the early diagnosis. ④ In combination with CT, MRI, CTA or DSA, B-US is of great benefit in the early diagnosis of liver cancer for both the nature of determination and localization ⑤ Fine needle aspiration for cytological assay or the diffusion way of the ethanol injected under ultrasonograph is also helpful for the establishment of the diagnosis.

The criteria for small liver cancer have not been standardized so far. In China, single nodular mass with the diameter or the sum of the diameters of two adjacent nodules less than 5cm was once regarded as small liver cancer. However, with the development of imaging tolls, the sensitivity is greatly increased. The liver cancers with the diameter less than 5cm are no longer regarded as small liver cancers clinically. The research in molecular pathology also showed that the great majority of liver cancers presented their biological features at the borderline of 3cm in diameter. Liver cancers with the diameter less than 3cm present the features of an early one, such as, growing largely in the swelling mode, cncapsulated, low incidence of vascular invasion and intra hepatic metastasis, diploid type of DNA contents and relatively slow growth. In contrast, the tumor with the diameter more than 3 cm has the capability of invasive growth and dissemination, the features of malignant biology and does not belong to the classical small liver cancer. In addition, as most of the liver cancer is homogeneous, tumor with more than two nodules has a higher probability of intra-hepatic metastasis. The concept that mononodular tumor with 3cm or less in diameter is a small liver cancer may be more suitable for the present liver cancer management and research. The early detection of liver cancer may significantly improve the efficacy of surgical

interventions. In our group[1], there was no surgical death in the 709 cases with the tumor diameter less than 5cm. The overall 1-year, 3-year and 5-year survival rates were 89.9%, 85.0% and 79.8%. Among them, of the 241 cases with 3cm or less in diameter, the overall one-year, 3-year and 5-year survival rates were 95.5%, 91.7% and 85.3% respectively. However, of the massive-sized liver cancers resected at the same period, they were 62.5%, 42.6% and 27.5% respectively.

THE HEPATECTOMY OF PRIMARY LIVER CANCER

At present, hepatectomy is still the treatment of choice for primary liver cancer. From 1960 to 1996[3], we performed 3932 cases of hepatectomy for liver cancer. Anatomical or extended hepatectomy accounted for 55.4% and local curative resection was 44.6%. The total mortality rate was 0.76% postoperatively, with 8.84% before 1997, 0.43% between 1978 and 1989 and 0.35% after 1990. The total 5-year survival rate was 36.1%, with 16.0% before 1977, 30.6% between 1978 and 1989 and 48.6% since 1990. One patient has survived more than 33 years. Comparing the survival rate listed above, we can tell that the efficacy of surgical intervention has been elvated significantly and rapidly since 1978. The main reasons are: the ability of early diagnosis was elevated; the renewal of some surgical concepts; the improvement of surgical techniques and perioperative management; and the development of comprehensive therapy postoperatively.

The pathological data from this group showed that 86.5% liver cancers were concomitant with cirrhosis or chronic hepatitis. The anatomical or extended hepatectomy might lead to a severe decompensated liver function. Therefore, the modality of liver resection drifted from a extended resection to an irregularly radical local one. Under the circumstance of chronic hepatitis or cirrhosis, the radical local resection not only increases the resectability, but also significantly decreases the surgical mortality rate and attains the same long-time therapeutic effects as the extended resection, or even better. The patients used to be subjected to conservative therapy when one or more complications presented, such as, jaundice, severe portal hypertension and esophageal varices with or without hemorrhage. With the accumulation of clinical practice, obstructive jaundiced patients resulting from involvement of hepatic hilus or cancerous thrombi invasion of biliary tract could undergo hepatectomy and the removal of biliary duct thrombi if hepatic cellular jaundice and other contra-indications could be ruled and most often, the jaundice disappeared gradually. To the patients with splenomegaly, hypersplenism and esophageal varices with or without hemorrhage, the hepatectomy can also be performed with splenectomy plus ligation of varices or portocaval shunts.

COMPREHENSIVE THERAPY FOR PRIMARY LIVER CANCER[4]

The comprehensive therapy was mainly focused on advanced liver cancers that were unresectable. But now, the concept of the comprehensive therapy for liver cancer is extended and includes ① the pre- and post-operative comprehensive therapy for resectable liver cancer to prevent the recurrence; ② palliative removal of incurably resected tumors followed by anti-cancer therapy in order to make the tumor shrink and prolong the survival time with tumor burden; and ③ comprehensive therapy for non-surgieal patients, with the hope of two-stage resection and long-time survival with tumor burden.

Comprehensive therapy includes surgical and non-surgical interventions. The former are hepatectomy, hepatic artery ligation (HAL), operative hepatic artery embolization (OHAE), drug delivery system (DDS), operative ethanol injection, microwave consolidation, laser gasification, freezing, etc. The latter are transcatheter arterial chemo-embolization (TACE), B-US directed percutaneous ethanol injection (PEI) or other drugs, radioisotopes and bio-agents, biotherapy, radiotherapy and traditional Chinese medicine.

Comprehensive therapy is so called with contrast to single method. Rational multimodality comprehensive therapy is superior to single method in terms of effects. The tetralogy method of surgical comprehensive therapy, which is the combination of HAL, OHAE, DDS and radiotherapy performed, in 603 advanced liver cancers in our hospital[2] showed that the rate of two-stage resection and one-year, 3-year and 5-year survival rate were significantly higher than that of single procedure (HAL or OHAE). The incidence of recurrence was only 7.4% in the 27 cases treated with comprehensive immuno-chemotherapy (cytokines plus low dose chemotherapy) after resection, while in control group, it was 32.0%. In 86 cases operated upon. DDS chemotherapy was adminiztered and the incidence of total one-year recurrence was 34.9%, while in hepatic artery group (n = 39), portal vein group (n = 26) and hepatic artery combining portal vein group were 33.3%, 34.6% and 23.6%, respectively. Non-surgical comprehensive therapy is indicative to almost all the unresectable liver cancer patients, with the methods of TACE and intra-tumor drug injection the most popular. In a series of 8 000 TACE cases, the 3-year survival rate was 13.9%.

The drugs was selected in the B-US directed local drug injection were absolute ethanol, ^{32}P radioisotope, OK432, TNF-α and IL-2. The 2-year survival rate in 700 patients receiving PEI was 80.0%, with a total of 3000 times treatment. In another group, 113 patients received TACE in combination with PEI, the tumors shrank in most patients (91.2%) at miscellaneous degrees, and the total 2-year survival rate was 81.6%. Among them, 11 of the 71 patients with monofocal large tumors received two[a2]stage resection after the tumors had shrunk and the two-stage resection rate was 14.28%.

Comprehensive therapy was not simply a random combination of miscellancous methods. If it was not properly combined, the therapeutic effects would be compromised. The design of the protocol should be case-specific. The model of the comprehensive therapy is multiple in literature. We propose two principles: ① attentions should be paid to the complimentary effects of each method. ② Avoiding the counteraction of the effects or the accumulation of side effects. At the same time, the toxic and negative effects of each method and its possible damage to the liver function should be paid enough attention. In addition, we stress the effects of traditional Chinese medicine in comprehensive therapy.

TWO-STAGE RESECTION OF PRIMARY LIVER CANCER[5]

In 1978, we reported a two-stage resection of a massive-sized liver cancer shrunk after HAL procedure. From then on, many reports followed and this procedure became a promising model for the unresectable large liver cancers. Surgical and non-surgical comprehensive therapies lead to the shrinkage of massive-sized liver cancers. At present, the documented methods for massive liver cancer shrinkage are: surgical comprehensive methods, such as HAL, OHAE and DDS, and non-surgical procedures, such as TACE, PEI, target therapy and radiotherapy. A rational combination of these methods makes some unresectable tumors resectable if they were successively employed. From 1974 to 1994, 649 patients received this therapy and 73 cases of them had their tumors resected with a resectability rate of 11.1% and no operative death. The 5-year survival rate was 61.5% postoperatively, with the longest survival being 17 years. The pathological data in this group showed that although the tumor shrank due to the comprehensive therapy, it was essential to remove the tumor because of the remnant living tumor cells. At present, though the reported two-stage resectability rates of liver cancer varies, the rates are still very low. The main causes of the low resectability rate are ① no general accepted criteria for tumor resectability. We propose that the two-stage resection is indicative only to the certainly unresectable tumors, otherwise, the one-staged removal is the first choice; ② rational employment of comprehensive therapy is crucial for the tumor shrinkage and ③ the unresectable liver cancers are recommended for non-surgical comprehensive therapy, such as TAE, PEI and guided chemoimmunotherapy as primary choice.

PROPHYLAXIS AND MANAGEMENT OF RECURRENCE[6]

The five-year recurrence rate in massive-sized liver cancers is 80%, while in small liver cancers, 40%-50%. The recurrence is most often found in liver, with few cases in bone, lung and brain or in abdominal cavity for the liver cancers ruptured before operation. The postoperative anti-recurrent comprehensive therapy, the early detection of the recurrent lesions and early management of the recurrent lesions are important steps to improve the therapeutic effects. Periodical postoperative follow-up is key to the early detection. We examine them with B-US, AFP and chest roentgenogram every 2-3 months. The patients with negative AFP are subjected to detection of other markers. The CT, MRI or CTA examinations are recommended to those highly suspected of recurrence. On the whole, the recurrence and metastases could be detected at subclinical stage. Comprehensive therapy is helpful in preventing the recurrence of liver cancer. The earliest recurrence happens within 2 months postoperatively, with the peak recurrence rate at 1-2 years. The recurrence after 5 years is rarely seen. Therefore, the anti-recurrent procedure should be given periodically in the 5 years after operation. Fine surgical manipulation to avoid medical dissemination, portal chemotherapy and suction of cancerous thrombi are all essential for prevention of recurrence. TACE, DDS, radiotherapy, immunotherapy and traditional Chinese medicine are given with detailed planning according to the condition of different patients. In recent years, we have employed immunochemotherapy, cytokines such as IFNs, TNF-α, TIL, CTL and some of them work well in anti-recurrence.

Reoperation is the treatment of choice for recurrent liver cancer. In this group, 123 patients received reoperation. The 1-year, 3-year, 5-year and 10-year survival rates after first resection were 99.2%, 71.4%, 53.2% and 19.1%. The 1-year, 3-year, 5-year survival rates after second resection were 83.5%, 38.2% and 19.6% while they were 94.7%, 44.9% and 25.0% after third resection. The reoperation of liver cancer is an effective

method for the improvement of 5-year survival rate and the establishment of reoperation concept has changed the idea that once the liver cancer recurred, it reached an advanced stage and was not fit for another operation. TACE and intra-tumor drug injection are indicative to those with poor liver function, hidden or multifocal lesions. In recent years, we performed PEI therapy in 109 recurrent cases with 0.7cm-15.2cm in diameter, averaging 4.6cm and the 1-year, 3-year and 5-year survival rates were 85.9%, 44.0% and 19.0% respectively. This procedure is easily performed and has the characteristic of faint side effects and damage.

CONSIDERATIONS FOR FURTHER IMPROVEMENT OF THE OUTCOME OF PRIMARY LIVER CANCER[8]

At present, several factors influence the prognosis of liver cancer clinically. They are ① whether small liver cancers detected early enough; ② pathological features of the liver cancer; ③ the curative degree of the resection; and ④ the efficacy of the anti-recurrent comprehensive therapy and the resectability of the recurrent lesions. For unresectable cases, the therapeutic effects depend on whether the comprehensive treatment is indicated and sensitive which will directly affect the survival and the two-stage resectability. To all of the liver cancer patients, the tolerance of the liver function to the long, successive traumatic therapy are the basis of therapeutic effects. Further improvement of therapeutic effects on liver cancer counts on the progress in basic liver cancer research. Recently, there were many progresses in the malignant biological features of liver cancer and new methods of biotherapy. The former includes clonal origin of liver cancer, oncogenes and enzymes related to the recurrence and metastasis of liver cancer and their mechanisms, glycoproteins and glycolipids research, the mechanism of the down-regulated immunity in liver cancer hosts and immune escape of liver cancer, induced differentiation of liver cancer, etc. The latter includes regimens that inhibit the recurrence and metastasis of liver cancer and angiogenesis inhibition therapy of liver cancer, specific active and passive immunotherapy, etc. Gene therapy and tumor vaceine technique are also developing rapidly.

It is controversial to the indications of liver transplantation on liver cancer. In advanced primary liver cancer, the recurrence after transplantation is unavoidable due to the vascular invasion and distal metastasis as well as immuno-suppressive agents used. On the contrary, the therapeutic effects of liver transplantation on small liver cancer combined with severe cirrhosis are corroborated. Comparing the therapeutic effects of hepatectomy and liver transplantation (60 cases each). Bismuth[9] concluded that the 3-year survival rates were almost the same, while the 3-year tumor-free survival rate was higher in liver transplantation group than in hepatectomy group. As to the small liver cancer (mononodular or binodular, with the diameter less than 3 cm), the results of liver transplantation were even better. Selby *et al*[10] showed that the overall 5-year survival rate in 105 unresectable cases of different stages that received liver transplantation was 36%, of whom the 5-year survival rate for one to three stage was up to 52.1%, while in stage four, it declined to 11%. They concluded that liver transplantation was fit for liver cancer in early stages ($\leqslant$2cm, no vascular invasion and no distal metastasis). However, we still could not regard liver transplantation as a routine therapeutic method due to high incidence of liver cancer, liver donation shortage and high cost.

With the accumulation of 30 years of clinical study, especially the research work during the past decade, we extended our knowledge in its biological characteristics, its clinical features and its diagnosis and treatments. The great efforts should be made for further improving the overall therapeutic results of liver cancer.

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