The value of postoperative hepatic regional chemotherapy in prevention of recurrence after radical resection of primary liver cancer

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INTRODUCTION

In China, primary liver cancer (PLC) ranks second in cancer mortality since the 1990s. In the field of PLC treatment, surgical resection remains the best, which includes large PLC resection, small PLC resection, re-resection of subclinical recurrence, as well as cytodestruction and sequential resection for unresectable PLC. However, recurrence and metastasis have become the major obstacles for further prolonging survival after resection. In authors’ institute, as reported in 1984, the 1-, 3-, and 5-year recurrence rates after curative resection were 17.1%, 32.5% and 61.5%, respectively \[1\]. Similar results were reported in 1993, being 15.0%, 45.5% and 55.3% \[2\]. Even after curative resection of small hepatocellular carcinoma (HCC), the recurrence rate remained high being 6.5%, 25.7% and 43.5% \[3\]. Therefore, recurrence and metastasis might be the next important targets to be studied. New strategies for the prevention of recurrence after curative resection become a key point to further improving the results of operation for PLC patients. In the literature, the opinion was preoperative transcatheter arterial chemoembolization (TACE) for resectable PLC could result in intrahepatic spreading and lung metastasis and could not improve the survival. Herein, the efficacy of postoperative hepatic regional chemotherapy in prevention of recurrence after radical resection for PLC was evaluated.

MATERIALS AND METHODS

The criteria for the curative resection were listed as follows: a. No distance metastasis was found in patients preoperatively. b. The tumor should be completely removed with the surgical margin from the tumor edge to the cut surface for over 0.5cm. c. The α-fetoprotein (AFP) level should return to normal within 2 months after resection for AFP positive patients and no residual tumors were detected by B-model ultrasonography and/or lipiodol-computed tomography (L-CT) at 2 months after resection for AFP-negative patients.

A total implantable port system was used for chemoembolization. The top of the system was inserted into hepatic artery proper via gastroduodenal artery without hepatic artery ligated during operation. Another system should be put into the main trunk of portal vein for patients with tumor embolus in portal vein or hepatic vein system. A four-day course of chemoembolization with 5 fluorouracil 750 mg-1000 mg, mitomycin C 8 mg-12 mg, cisplatin 80 mg and Ultralipiodol 5 mL was performed at 4-6 weeks postoperatively. For patients with tumor embolus in the portal vein or hepatic vein system, the drugs were equally injected via the two catheters, while the lipiodol was given via the hepatic artery only. The regional hepatic chemotherapy will be repeated at regular interval of 2-4 months thereafter.

After discharge from the hospital, all the patients were closely followed up: every 2-3 months during the first 2 postoperative years and 6-months intervals thereafter. Follow-up comprised a clinical examination, conventional liver function tests, serum AFP level assayed, ultrasonography and chest X-ray. Lipiodol-CT were done at 2-3 weeks after each time of chemoembolization. When recurrence and/or metastasis were suspected, examinations including CT, MRI and bone scan were taken. The diagnosis of recurrence or metastasis were decided according to the positive imaging examinations.

A total of 105 patients having a histologically verified PLC met all the above-mentioned criteria from January 1995 to December 1997 at Shanghai Liver Cancer Institute. The median age of the entire series was 52 years (range, 30-73 years) and the median diameter of the tumor was 6.8 cm (range, 1999-06-30 Accepted 1999-09-18
1cm - 18.8 cm). The male to female ratio was 5.5:1. Among these patients, ninety two patients (87.6%) combined with posthepatic cirrhosis and seventy patients had positive AFP level. As to the number of tumor, it was found 76 patients with single nodule, 19 with two nodules and 10 with three to six nodules. Five patients had visible tumor embolus in the second branch of portal vein and one patient had tumor embolus in the right hepatic vein. The average time of chemoembolization given to patients was 3.4 times (range, 1-7 times).

Statistical analysis: the difference between different groups were tested by χ² test.

RESULTS

All patients were followed up for 4 - 40 (x±s = 22.7±9.7) months. Two patients without recurrence died of severe hepatitis at 12 or 13 months, respectively. In the remaining 103 patients, recurrence in the remnant liver was found in 11 patients, metastasis to the lung in 1 patient and implantation in the abdominal cavity also in one. The recurrence rates of 1-, 2-, 3- years were 1%, 15% and 18%, respectively. The interval between recurrence and operation varied from 10 to 20 (x±s = 15.2±2.9) months. Another two patients had a second primary tumor in the breast and lung. For the treatments of the 13 recurrent patients, a second resection was done in 9 patients, hepatic regional chemoembolization plus percutaneous intratumor ethanol injection was done in the other four patients, who could not tolerate the second operation. Neither recurrence nor metastasis was found in six patients with tumor embolus in portal vein or hepatic vein.

The recurrence rates of different groups are shown in Table 1.

| Items      | No. | Recurrence rate (%) |
|------------|-----|---------------------|
| AFP        |     |                     |
| Positive   | 70  | 12.9                |
| Negative   | 35  | 11.4                |
| Tumor      |     |                     |
| >5cm       | 45  | 13.3                |
| <5cm       | 60  | 11.7                |
| Nodules    |     |                     |
| Single     | 74  | 12.2                |
| Multiple   | 31  | 12.9                |

DISCUSSION

The following causes might be involved for the recurrence after curative resection for PLC: a: There existed undetectable intrahepatic spreading or long distance metastasis. b: A metachronous and unrecognized synchronous multifocal primary tumor may be responsible for recurrence. c: The procedure of operation can make tumor cell detached and spread in the liver. So, curative resection doesn’t mean all the tumor cells being totally removed. The depressed immune system’s function of PLC patient can not guarantee that all the residual tumor will be killed even under the condition of combining with oral or one shot of hepatic chemotherapy via the hepatic artery. Systemic chemotherapy is abandoned in prevention of recurrence for it can not only damage the immune function of the patient but also can not guarantee the effective drug concentration at the target organs. Contrast to the systemic chemotherapy, hepatic regional chemotherapy given via hepatic artery and/or portal vein can result in a high drug concentration in the target organ without severe damage to the immunologic function.

No significance difference was found between AFP-positive patients and AFP-negative patients and between large PLC and small one and between patients with single or multiple tumor nodules (Table 1). Take into consideration that the short time recurrence rates of large PLC, multiple PLC and PLC with tumor embolus in the portal vein or hepatic vein were not higher than those of small PLC, PLC with single nodule and PLC without tumor embolus, our results indicated that postoperative hepatic regional chemotherapy can significantly decrease the short time recurrence rate after curative resection for these patients.

The peak recurrence time for PLC was within two years after curative operation. The resection for PLC and depress the patients’ immune function and stimulate secretion of some regeneration related factors. These changes can make residual tumor cells and precancerous cell fast dividing and more sensitive to chemotherapy. So, it is a good chance for patients to receive postoperative hepatic regional therapy once the liver function and immune function return to normal level. It should be emphasized that if the liver function and immune function have not returned to normal, too early chemotherapy could result in further damage to patients. In general, the first time chemoembolization should be taken at 4-6 weeks after curative resection and repeated at regular interval of 2-4 months thereafter until the patients survive over the peak recurrence time. The interval of chemoembolization can be prolonged under the closing of follow up and without positive signs which indicating recurrence.

Our results indicate that auxiliary hepatic regional chemotherapy after curative resection can significant decrease the recurrence rate during the peak recurrent time. Considering that chemotherapy can neither kill tumor cell completely
nor can permanently prevent new tumor foci occurring in the remnant liver. It is no doubt that hepatic regional chemotherapy can’t effectively prevent recurrence of PLC permanently. Repeated chemotherapy via hepatic artery can occlude the hepatic artery and damage the liver function. Most patients’ port system can maintain in good condition for only about one year, this may contribute to the higher recurrence rates in the later two years as compared to that of the first year. Other multimodality treatment, such as immunotherapy, should be used in combination to further reduce the recurrence rate after curative resection.

REFERENCES
1 Tang ZY, Yu YQ, Zhou XD. An important approach to prolonging survival further after radical resection of AFP-positive hepatocellular carcinoma. J Exp Clin Cancer Res, 1984;3:359-368
2 Zhou XD, Yu YQ, Tang ZY, Yang BH, Lu JZ, Lin ZY, Ma ZC, Xu DB, Zhang BH, Zheng YX, Tang CL. Surgical treatment of recurrent hepatocellular carcinoma. Hepatogastroenterology, 1993;40:333-336
3 Kanematsu T. Is postoperative chemotherapy effective for the prevention of recurrence after surgery for hepatocellular carcinoma. Hepatogastroenterology, 1996;43:1404
4 Kohno H, Nagasue N, Hayashi T, Yamamino A, Uchida M, Ono T, Yukaya H, Kimura N, Nakamura T. Postoperative adjuvant chemotherapy after radical hepatic resection for hepatocellular carcinoma (HCC). Hepatogastroenterology, 1996;43:1405-1409
5 Michalopoulos GK, Defrances MC. Liver regeneration. Science, 1997;276:60-66