

Clinical Observations

A STUDY OF INTRAOPERATIVE TREATMENT MODALITIES FOR NONRESECTABLE PRIMARY LIVER CANCER: A FOLLOW-UP OF 200 CASES

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This paper reports the results of intraoperative treatments with different modality in 200 patients with nonresectable primary liver carcinoma (PLC) from April 1964 to July 1993 in our hospital. PLC was verified histologically in all cases. They were divided into 2 groups according to the methods of treatment. In group I, 115 cases received anticancer agents by hepatic artery infusion (HAI). The 1- and 2-year survival rates were 10.4% and 1.7%, respectively and only one patient survived for 65 months. In group II, 85 cases received multimodality treatments (MMT) with various combination of hepatic artery chemoembolization (HACE), hepatic artery ligation (HAL), microwave coagulation of tumor (MWC) and ethanol injection into tumor (EIT). The 1-, 2-, 3- and 5- survival rates were 34.1%, 21.2%, 12.0% and 6.7%, respectively. 5 cases survived for 41 to 63 months. The tumor was resected at second stage in 6 cases after MMT. The results suggest that MMT is an effective approach to improve the long-term survival of patients with nonresectable PLC.

Key words: Liver neoplasm, Surgery, Therapy, Embolization

At present, the multimodalities treatments (MMT), the various combinations of hepatic artery chemoembolization (HACE), hepatic artery ligation

(HAL), tumor coagulation with microwave (MWC) and ethanol injection into tumor (EIT) were more effective than hepatic artery infusion (HAI) with anticancer agents for nonresectable primary liver cancer (PLC). These measures have improved the prognosis of patients with advanced PLC. The results of different treatment for 200 cases with nonresectable PLC. The results of different treatment for 200 cases with nonresectable PLC during laparotomy from April 1964 to July 1993 in our hospital are reported as follows.

MATERIALS AND METHODS

In these 200 cases with nonresectable PLC, 189 were male and 21 were female. The ratio of male to female was 9: 1. The age of these cases ranged from 23 to 71 years old with average of 47.6. Hepatocellular carcinoma was verified in 181 cases; cholangiocellular carcinoma in 11 cases; mixed type in 3 cases and other type in 5 cases. Of them, 83.0% (166/200) were associated with hepatic cirrhosis and 69.1 (132/191) with positive HBsAg. The sites of cancer were in left lobe in 28 cases, right lobe in 102 cases, hepatic hilus in 39 cases and both lobes in 31 cases. 6 cases were in subclinical stage (3%, 6/200); 176 in moderate stage (88%, 176/200) and 18 in advanced stage (9%, 18/200). All cases were divided into two groups

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according to the methods of treatment.

115 cases were in group I and underwent only HAI. 5-Fu 1000 — 1500 mg, MMC 8 — 10 mg and ADM 40 — 60 mg were injected through right gastroenteral artery or right gastric artery for only one time in 28 cases. The catheter in the artery was reserved in 87 cases, through which anticancer agents were administered periodically. 5-Fu was given in 33 cases with total amount of 3000 — 8000 mg; TSPA in 22 cases with total amount of 150 — 200 mg; Sb₇₁ in 22 cases with total amount of 500 — 1000 mg; CTX in 7 cases with total amount of 4000 — 8000 mg; MMC in 6 cases and other agents in 4 cases.

85 cases in group II and underwent MMT. 1) 21 cases received HACE with emulsion of Lipiodol 8 — 10 ml, ADM 50 — 70 mg and MMC 6-10 mg. 17 of whom received gelform powder (GEL) in addition to the emulsion. 2) 13 cases underwent both HACE and HAL, ligation of right branch of hepatic artery in 7 cases and ligation of left branch of hepatic artery in 1 cases and ligation of hepatic artery itself in 5 cases. 3) 27 cases underwent EIT. The right branch of hepatic artery was ligated after injecting 5 — 8 ml ethanol through this artery in 4 of them. HACE and EIT were administered in 14 of them. In addition, MWC was adopted in remaining 9 cases because of limited amount of ethanol and insufficient necrosis of these large tumors with EIT. 4) 24 cases under went MWC,

which was administered to coagulate the tumor with 1 cm interval of needle span with different lengths of microwave needles. Satellites were discovered during laparotomy in 5 cases, who was administered with MWC after HACE and HAL. The tumor in 6 cases invaded the hepatic hilus or inferior vena cava. The tumor area near those large vessels was administered with EIT in order to avoid injure of them and bleeding by MWC.

RESULTS

All cases were followed up until July 1995 and the survival results were showed in Table 1 and 2. In group I (HAI), the 1-, and 2-survival rates were 10.4% and 1.7%, respectively and only 1 patient survived for 65 months. In group II, the 1-, 2-, 3- and 5- survival rates were 34.1%, 21.2%, 12.0% and 6.7%, respectively. 5 cases survived for 41 to 63 months. The tumor was resected in 6 cases after MMT. These results indicate that the effect of MMT was significantly better than that of only HAI ($P < 0.05$). 4 cases died within 1 month postoperatively with a postoperative mortality rate of 2.0%. The causes of death were hepatic failure in 2 cases, hemorrhage of upper gastrointestinal tract in 1 case and ethanol toxication in 1 case (Table 1,2).

Table 1. Intraoperative treatment models and results of 200 cases of nonresectable PLC

Treatment model	Survival rates (%)					still alive	Two-stage resection	Operative Death
	No	1 year	2 years	3 years	5 years			
HAI	115	10.4 (12/115)	1.7 (2/115)	0.9 (1/115)	0.9 (1/115)	0	0	3
HACE and GEL	21	23.8 (5/21)	9.5 (2/21)	5.6 (1/18)	0.0 (0/10)	1	1	0
HACE and HAL	13	38.5 (5/13)	23.1 (3/13)	16.7 (2/12)	10.0 (1/10)	1	2	0
EIT or/and MWC	27	40.8 (11/27)	33.3 (9/27)	16.7 (4/24)	5.3 (1/19)	2	1	1
HACE, HAL MWC or/and	24	33.3 (8/24)	20.8 (5/24)	9.5 (2/21)	11.8 (2/17)	1	2	0
HACE, HAL EIT								
Total	200	20.5 (41/200)	10.5 (21/200)	5.3 (10/190)	2.9 (5/175)	5	6	4

Table 2. Results of HAI and MMT

Group	No.	Survival Rates (%)				Still alive	Two-stage resection	Operative death
		1 year	2 years	3 years	5 years			
HAL	115	104	1.7	0.9	0.9	0	0	3
MMT	85	34.1	21.2	12.0	6.7	5	6	1

DISCUSSION

1. The prognosis of PLC was poor. More than 0.11 million people died from PLC in our country each year.¹ The rate of tumor resection was low and the recurrent rate was very high postoperatively for PLC patients. Luo² reported in 1993 that over half patients with PLC recurred with 2 years after radical hepatectomy. The effect of general chemotherapy was rather poor. Miyazaki³ reported in 1988 that the patients with IV stage survived only 29 days after general chemotherapy. The concentration of anticancer agents in tumor given through hepatic artery was much higher than that given through peripheral veins, which resulted in improved effects and less side effects and became an important approach for moderate and advanced PLC patients. Nevertheless, our study as well as other literature indicated that the effect of HAI was not so satisfactory. The effect of palliative resection was not so good as that of palliative surgical treatment.^{2,4} The palliative treatments such as cryotherapy in 1970's laser vaporization in 1980's and MMT of HACE in combination with HAL, MWC and EIT have greatly improved the prognosis for PLC patients and were widely administered.⁵⁻⁸ The large and unresectable PLC could become small PLC and then be resected at second stage after MMT and if necessarily, TAE, BRM, radiotherapy, immunotherapy and so on after operation.

2. In recent ten years, intraoperative HACE, HAL, EIT and MWC have become main approaches for palliative surgical treatment of PLC. Now the tendency is how to make full use of each principle and learn from other strong points to offset its own weakness and combine them reasonably.

Usually about 90% blood supply of liver carcinoma come from hepatic artery and 25% blood supply of normal liver tissue come from it. Therefore,

HACE or HAL could result in wide necrosis of tumor tissue and normal liver tissue could tolerate such treatments. Owing to the siphon of blood vessels inside the tumor, the lipiodol concentrate in and embolize the microvessels of the tumor, which in combination with the chemotherapy of anticancer agents induce the deoxygen and necrosis of tumor cells. Due to the influence of the distribution tumor artery, arterovenous fistula and the gravity of lipiodol, the distribution of lipiodol inside the tumor often appeared unequal, especially in the border and postsuperior part of the tumor whose blood supply mainly come from portal vein. The residual tumor often develops postoperatively. Therefore, it might get better effects. If HACE is combined with HAL, EIT and MWC to eliminate the residuary tumor.

The advantages of EIT are as follow. 1) Ethanol could destroy the endothelium of microvessels, make protein degenerate and then embolize the microvessels for long term. In addition, the bypass circulation could be hardly established.³ 2) Pure ethanol injected directly into tumor could bring about coagulative degeneration and necrosis of the tumor. 3) Pure ethanol is good hemostatic which could stop bleeding from ruptured tumor with EIT. However, ethanol is also a kind of toxicant, the catheter through which the ethanol is injected should be inserted into the artery which bring blood to tumor itself and the velocity of injection should be slow to avoid ethanol into general circulation. The amount of ethanol injected every EIT must limited to not more than 60 ml. Overdosage of EIT might cause death. Immediate toxic reaction manifests slow down of heart rate, which could sharply reduce from 80 — 90 bpm to 30 — 40 bpm within several minutes, atropine should be administered promptly in such condition and ECG, heart rate and respiratory rate should be monitored continuously with anesthetic machine. Hemoglobinuria may present in 12 hours after EIT and usually disappear in 24 hours automatically. Owing to

the limit amount of ethanol when the tumor is too large, EIT could get better effect if it combined with HACE, HAL and MWC.

The principle of MWC to treat PLC is mainly its thermal effect on tumor cells. The tumor tissue absorb radiation of microwave to produce vibration of water with high speed, which changes into heat energy to make tumor tissues coagulate.⁴ The temperature inside the tumor may reach to 60 °C and the tumor cells thus could be killed effectively and permanently. Whole tumor tissue might be abolished if to coagulate the tumor with about 1 cm interval with different lengths of microwave needles. MWC as well as EIT usually has no postoperative complications such as hemorrhage, bile leakage, and infection. It certainly became an effective and safe therapeutic weapon.

Up to now, nonresectable PLC still constitute majority who have indication of laparotomy. How to combine with each therapeutic method had no fixed model yet. We should apply different approaches effectively according to the size and location of tumor, accompanied with cirrhosis and so on in order to wipe out tumor to a maximum, to preserve normal liver tissue as much as possible and to improve the prognosis. How to get the most suitable combination

model of such therapeutic method still need to study.

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