

RAPID COMMUNICATION

Comparison of therapeutic effectiveness of combined interventional therapy for 1126 cases of primary liver cancer

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effect of TACE and RFA is better than that of TACE, and the effect of TAI is minimal.

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Key words: Hepatocellular carcinoma; Transcatheter arterial chemoembolization; Combined interventional therapy; Survival analysis

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Abstract

AIM: To verify the effect of combined interventional therapy for hepatocellular carcinoma (HCC).

METHODS: The clinical data of 1126 HCC patients who received combined interventional therapy for transcatheter arterial chemoembolization (TACE) before or after hepatectomy, TACE and radio-frequency ablation (RFA), Chinese medicine treatment and biotherapy after TACE or transcatheter arterial infusion (TAI), were reviewed according to the results of their liver function, alpha-fetoprotein, image data, color-ultrasonography finding and survival rate.

RESULTS: A total of 874 patients were followed up for a period of 2 to 63 mo. The overall 1-, 3- and 5-year survival rates were 67.8%, 28.7% and 18.8% respectively. The 1- 3- and 5- year survival rates of patients who received TACE were 74.7%, 41.4%, 36.9% before hepatectomy and 78.9%, 40.4%, 37.5% after hepatectomy. The effective rate (PR + NC) after TACE and RFA was 93.4%, the 1- and 3- year survival rates were 74.5% and 36.8% after TACE and RFA. The effective rate of PR + NC after TACE was 83.2%. The 1-, 3- and 5- year survival rates were 69.3%, 21.7%, 8.4% after TACE. The effective rate of PR + NC after TAI was 27.5%, the 1- and 2- year survival rates were 11.6% and 0% after TAI. The liver function, color-ultrasonography finding and alpha-fetoprotein after TACE + RFA, TACE and TAI were compared. There was no significant difference in each index between TACE and RFA or TACE as well as in liver function between TACE and RFA or between TACE and TAI.

CONCLUSION: The therapeutic effectiveness of TACE before or after hepatectomy is most significant, while the

INTRODUCTION

Transcatheter arterial interventional therapy is extensively used in treating hepatocellular carcinoma (HCC). To reduce the intra-hepatic recurrence and improve the protective efficacy after treatment for HCC, some scholars have proposed combined interventional therapy as a choice of treatment for HCC^[1]. We analyzed the therapeutic effectiveness of different combined interventional therapies for HCC according to the survival rate, liver function, image data and indications of tumor.

MATERIALS AND METHODS

Patients

A total of 1126 patients were retrospectively studied from January 1994 to October 2003. Of them, 873 were males and 253 were females (aged 32-76 years, mean 56.2 years). The patients were treated following the HCC Clinical Diagnosis and Staging Standard stipulated at the 8th National Academic Conference of Liver Cancer in September 2001. Among these patients, 78 had a family history of liver cancer, 985 had a medical history of serum hepatitis, 48 had a medical history of hepatitis C, 342 had cardinal symptoms of right upper quadrant pain, 336 felt epigastric distention after dinner or suffered from anorexia, 162 had low fever accompanied with progressing wasting, 286 exhibited no overt symptoms. Prior to the treatment, AFP was greater than 20 ng/mL in 735 cases, greater than 400 ng/mL in 521, negative in 227, unknown in 164. A total of 874 patients were followed up for 2

Table 1 Clinical data of 1126 patients

Group	Cases (n)	Size of tumor (cm)			Clinical staging			Liver function level		
		<5	5-10	>10	I	II	III	A	B	C
Preop. TACE	258	20	145	93	104	154	0	155	103	0
Postop. TACE	154	9	76	69	16	138	0	83	71	0
TACE + RFA	126	3	57	66	48	57	21	92	34	0
TACE	469	31	239	199	156	251	62	252	197	20
TAI	119	11	47	61	28	47	44	14	73	32
Total	1126	74	564	488	352	647	127	596	478	52

Table 2 Clinical data of 1126 patients

Group	Cases (n)	Karnofsky scores		HBsA	AVF		Embolus in PV	
		0-80	80-100	(+)	HV	PV	Right	Left
Preop. TACE	258	172	86	221	9	19	67	73
Postop. TACE	154	98	56	124	4	10	21	16
TACE + RFA	126	83	43	107	12	27	32	26
TACE	469	291	178	412	76	125	106	92
TAI	119	78	41	101	22	34	32	28
Total	1126	722	404	965	123	215	258	235

to 63 mo (averaged 26.3 mo). Combined interventional therapy was given, including transcatheter arteria hepatica chemoembolization (TACE) before or after hepatectomy, radio-frequency ablation (RFA) after TACE, Chinese medicine treatment and biotherapy after TACE or transcatheter arteria hepatica infusion (TAI). The clinical data of various kinds of combined interventional therapy for HCC are shown in Tables 1 and 2.

TACE

Twelve mg mitomycin (MMC) and 1.0 g 5-FU were diluted in 60 mL sodium chloride solution respectively and infused through a catheter. Then 50 mg epirubicin (EPI) and iodinated oil were compounded into a mixed emulsifier and infused into the blood-supply artery of the tumor through a catheter. Then, the artery was embolized with granules of spongia gelatinosa.

TAI

Fifty mg EPI, 12 mg MMC, and 1.0 g 5-FU were diluted in 60 mL sodium chloride solution respectively and infused through a catheter into the blood-supply artery of tumor. HCC patients treated 3-4 times with TACE at 1-2 mo intervals after hepatectomy, if pathological report showed remnant cancer cells on the cutting edge or AFP > 20 ng/mL or the image showed remnant tumor. Those who lost the chance of one-stage operation were treated with TACE and underwent re-examination of CT after 1-2 mo. If iodinated oil deposited in the tumor was reported to be coarctate, the volume of tumor was decreased or the normal liver had compensatory hyperplasia, the patients underwent hepatectomy after their recuperation. Those who did not recuperate or rejected hepatectomy were treated with RFA 3-4 wk after TACE. On the first day after TACE or TAI, the patients were treated with the following Chi-

Table 3 Accumulated survival rate for 874 HCC patients after various kinds of interventional therapy

Group	Cases (n)	1 yr		3 yr		5 yr	
		Cases (n)	Survival rate (%)	Cases (n)	Survival rate (%)	Cases (n)	Survival rate (%)
Preop. TACE	198	148/198	74.7	82/198	41.4	58/157	36.9
Postop. TACE	114	90/114	78.9	46/114	40.4	33/88	37.5
TACE + RFA	106	79/106	74.5	39/106	36.8	-	-
TACE	387	268/387	69.3	84/387	21.7	26/309	8.4
TAI	69	8/69	11.6	0/69	0	0/69	0
Total	874	593/874	67.8	251/874	28.7	117/623	18.8

nese herbal medicines: 30 g Milkvetch Root, 20 g Dangshen, 15 g Largehead Atractylodes Rhizome, 15 g Indian Bread, 30 g Huaishan, 15 g Finger Citron, 15 g Bupleurum chinense, 15 g Danshen Root, 3 g Radix Notoginseng, 15 g Virgate Wormwood Herb, 20 g Tianjihuang, 20 g Canton Love-Pea Vine, 5 g Radix Glycyrrhizae. The herbal medicines were decocted in water for oral dose once daily for 3-4 wk as a course of treatment. After 3-5 d, the patients received intramuscular injection of 1000 U interferon once a day for 20 d as a course of treatment.

Follow-up

The liver and renal function, AFP, blood RT, KPS scores were re-examined, and sonography, CT, chest X-Ray were performed once a month, and then every 3 mo during the follow-up period. The date on which the patients lost their follow-up was regarded as the date of death. According to the WHO evaluation standard of therapeutic effect of solid tumor (1981), the patients who were treated with TACE + RFA, TACE and TAI were categorized into 4 degrees: complete remission (CR), partial remission (PR), no change (NC) and progression (PD). The first 3 degrees were considered efficient and the last degree was considered inefficient.

Statistical analysis

SPSS12.0 was used for statistical analysis. The survival rate was evaluated by adopting probability ratio multiplication theorem, and chi-square test was used for comparison between the 2 groups. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 874 cases were followed up for 1-7 years. Comparison of the accumulated survival rate after various kinds of combined interventional therapy is shown in Table 3. The therapeutic effect of interventional therapy in 562 patients is shown in Table 4. Changes of liver function, tumor blood-supply and AFP in 562 cases after interventional therapy were compared. Fifteen days after combined interventional therapy, color Doppler was used to detect the blood flow around and inside the tumor. The change in recovery rate of AFP before and after TACE + RFA, TACE and TAI was compared. The results are shown in Table 5.

Table 4 Therapeutic effect of TACE+RAF, TACE and TAI in 562 patients

Group	Cases (n)	PR	NC	PD	Effective rate (%)
TACE + RFA	106	73	26	7	93.4
TACE	387	276	46	65	83.2
TAI	69	8	11	50	27.5
Total	562	357	83	122	81.5

Table 5 Changes of indexes before and after interventional therapy n (%)

Group	Index			
	Degrade of Child liver function	Blackout of blood flow inside tumor	Blackout of blood flow around tumor	Recovery of AFP
TACE + RFA	33/106 (31.1)	59/106 (55.7)	54/106 (50.9)	49/106 (46.2)
TACE	119/387 (30.7)	212/387 (54.8)	189/387 (48.8)	174/387 (45.0)
TAI	23/69 (33.3)	0/69 (0)	0/69 (0)	0/69 (0)
Total	175/562 (31.1)	271/562 (48.2)	243/562 (43.2)	223/562 (39.7)

DISCUSSION

At present, hepatectomy remains the preferred method to treat primary liver cancer. Second-stage hepatectomy after TACE is a great breakthrough in the field of liver cancer treatment after hepatectomy of macro-hepatoma in the 1950-1960s and micro-hepatoma in the 1970s^[3]. TACE after radical excision of hepatoma can efficiently kill remnant cancer cells, decrease recurrence and increase survival rate remarkably^[4,5]. However; it was reported that TACE can damage hepatic and immunologic function, thus decreasing the survival rate^[6]. Zheng *et al*^[4] retrospectively analyzed the therapeutic results of 420 HCC patients after combined therapy, and found that the 1- and 3-year survival rates of non-angioencroached HCC patients after treated with TACE are 100% and 60% before radical excision, 77.8% and 22.2% before palliative excision, respectively, higher than those of the patients not treated with TACE before hepatectomy, and there is no significant difference between TACE before and after hepatectomy. Wang *et al*^[7] reported that the 1-, 3-, 5- year survival rates of 20 HCC patients after treated with combined therapy are 95.0%, 63.5%, 32.9% after second-stage hepatectomy, suggesting that the 1-, 3-, 5- year survival rates after TACE before or after hepatectomy are the highest. The reasons may be as follows: some of the 1126 cases treated with TACE before or after hepatectomy had hepatic AVF and embolus of hepatic portal vein, only interventional therapy was given before hepatectomy, and TACE treatment did not continue with double-chemoembolization or internal radiation. All these indicate that cancer cells can extend to distal ramulus along homonymous portal vein during operation procedures. Though macroscopic circumscription of hepatectomy is satisfactory, there are remnant cancer cells on the cutting edge, and liver cancer

complicating hepatic cirrhosis limits circumscription of hepatectomy. The above-mentioned factors are the major reasons for recurrence which is an important reason for the low survival rate after hepatectomy. For this reason, it is necessary to treat HCC patients with TACE combined with Chinese medicine and biotherapy to increase their immunologic function after hepatectomy. To effectively increase the survival rate, HCC patients should be treated with double-chemoembolization or internal radiation before hepatectomy.

Combined interventional therapy including TACE, TAI, RAF, percutaneous intra-tumor absolute alcohol injection (PEI), percutaneous intra-tumor acetic acid injection (PAAI), percutaneous intra-tumor hot saline water injection (PSI), percutaneous cryotherapy (PCT), is dominantly used in non-surgical treatment of HCC. Except for TACE and TAI, extra-hemal and circumscriptus "interstitial substance therapy"^[8] can treat HCC through different mechanisms. It was reported that chemoembolization can reduce the number of newly generated tumor vessels and the remnant tumor may generate new vessels through various ways^[9]. To increase the life span, we believe that HCC patients should be treated with RFA, PEI, PAAI, PSI, and PCT on the basis of TACE to kill remnant cancer cells. Liu *et al*^[10] reported that the 1-, 2-, 3- year survival rates of HCC patients after treated with TACE are 59.52%, 22.06% and 14.34% , while the 1- and 3- year survival rates of HCC patients after treated with TAI are 27.94% and 0%. In our study, the 1-, 2-, 3- year survival rates of 387 patients after treated with TACE were 69.3%, 21.7% and 8.4% respectively, and the 1- and 3- year survival rates of 69 after treated with TAI were 11.6% and 0%, suggesting that combined interventional therapy for HCC is influenced by many factors.

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