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The Indications for Tumor Mass Reduction Surgery and Subsequent Multidisciplinary Treatments in Stage IV Hepatocellular Carcinoma

MASAYUKI YAMAMOTO, HIDEHIKO IIZUKA, MASANORI MATSUDA, KAORU NAGAHORI, KAZUO MIURA, and JUN ITAKURA

The First Department of Surgery, Yamanashi Medical College, Tamahocho, Yamanashi, 409-38 Japan

Abstract: The indications for tumor-mass reduction surgery and subsequent immunotherapy in patients with stage IV hepatocellular carcinoma (HCC) were elucidated in this study. About 42% of the resected specimens from stage IV-A patients (n = 26) contained well-differentiated multicentrically occurring HCC, which was not found in any of the stage IV-B patients (n = 9). The 2-year survival rate after reduction surgery was 49% for the stage IV-A patients and only 13% for the stage IV-B patients, while 6 of the stage IV-A patients who survived for more than 2 years had no vascular invasion or distant organ metastases. Some of the stage IV patients maintained normal peripheral natural killer (NK) activity and were also able to tolerate surgical insults immunologically, provided that appropriate postoperative immunotherapy was given. Thus, stage IV-A HCC has a greater possibility of containing slow-growing intrahepatic tumor clusters, and the removal of any rapidly growing tumors from among these should be undertaken by reduction surgery followed by subsequent multidisciplinary treatment for residual tumor cells, including appropriate immunotherapy.

Key Words: hepatocellular carcinoma, reduction surgery, NK activity, multidisciplinary treatment

Introduction

The early detection of smaller tumors and their immediate resection is of primary importance in the treatment of hepatocellular carcinoma (HCC). However, in many cases it is not possible to undertake curative resection because of multiple intrahepatic involvement, vascular invasion, and/or distant organ metastases. According to the International Union Against Cancer (UICC) macroscopic staging of primary malignant hepatoma,[1] we attempted to retrospectively analyze the effects of reduction surgery on the postoperative survival of patients with stage IV HCC. Since 1985, tumor-mass reduction surgery with subsequent multidisciplinary treatment, including transcatheter arterial embolization (TAE), chemoembolization, and/or immunotherapy has been performed in 35 stage IV HCC patients in our department. This reduction surgery is aimed at decreasing target tumor-cells so that effective postoperative treatment can be carried out. It is also performed to prevent ruptures of HCC and relieve the obstructive jaundice and abdominal distension caused by large tumors. In the present paper, by reviewing these 35 cases, the indications for reduction surgery in stage IV HCC patients and the roles of postoperative multidisciplinary treatment, particularly immunotherapy, are discussed from the viewpoint of tumor characteristics and host immunity.

Patients and Methods

The clinical features of 26 patients with stage IV-A HCC and 9 patients with stage IV-B HCC who underwent tumor-mass reduction surgery at the First Department of Surgery, Yamanashi Medical College, between 1985 and 1990 are shown in Table 1. As a comparison, the clinical status of 11 stage IV HCC patients who received only hepatic arterial cannulation is also shown.

Reduction surgery was carried out to remove intrahepatic tumors without incising them. No definite decisions were made in the early period about which of the multiple tumors were to be resected, but in all cases large tumors occupying more than one segment were excised. Liver resection of less than one segment (Hr1>) was performed to remove areas containing

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small tumors that showed no tumor stain on hepatic arteriography, suggesting that the effect of TAE on them was limited. Furthermore, from 3 years ago, when cytotoxic T lymphocyte (CTL)[2] infusion was initiated as an adoptive immunotherapy, reduction surgery was also considered indicative to obtain tumor cells. The rate of removing intrahepatic tumors by reduction surgery was calculated as: (maximum diameters of resected tumors/maximum diameters of all tumors) × 100. Diameters were measured by preoperative ultrasonography (US).

US-guided ethanol injection was another intraoperative treatment used to reduce the tumor mass, given in 16 cases for tumors remaining in areas unresectable by reduction surgery. All patients underwent cholecystectomy to prevent cholecystitis, which often occurs following TAE or hepatic arterial infusion chemotherapy. To achieve better results from the postoperative treatment, blood supply to the remaining liver tumors was reduced by ligating the collateral arteries and severing the surrounding ligaments between the liver and the diaphragm. In 19 patients, intra-arterial cannulation into the proper hepatic artery or its branch was performed via the gastroduodenal artery or a branch of the hepatic artery to irrigate the resected liver during the operation. The other end of the cannula was connected to a subcutaneously implanted port (Infuse-a-port, Infusaid, Mass.) or infusion pumps (Infusaid, Infusaid), in 18 patients, and a portable extracorporeal pump (PSW-31, Nikkiso, Japan) in 1 patient.

Multicentricity of Intrahepatic Multiple Tumors

The multicentric occurrence of HCC[3–5] was determined according to the following histological criteria: (1) remote and smaller nodules showing microscopically well-differentiated HCC, despite more poorly differentiated HCC in the major nodules; (2) multiple well-differentiated HCCs; and (3) one of multiple HCCs showing the "nodule-in-nodule" form.[6]

Pre- and Postoperative Immunity of Stage IV HCC Patients

The preoperative natural killer (NK) activity in peripheral blood was measured in 46 HCC patients admitted to our department in 1989 and 1990, by a ^{51}Cr-releasing assay, using the leukemic cell line, K 562, as target cells.[7,8] The controls comprised ten healthy volunteers over 40 years old, with a mean age of 47.2 ± 4.3 years. The NK activity in these patients was compared with respect to the macroscopic and clinical stage.[9] The postoperative changes in NK activity were measured every week after surgery in the following two groups

Table 1a. Clinical features of Stage IV HCC patients who underwent liver resection

	n	Age (mean ± SD)	Sex M/F	Metastasis		Clinical stage	Image V_P	Image V_V	Liver resection	Intraoperative: Ethanol injection	Intraoperative: Hepatic art. cannulation	Postoperative: TAE alone	Postoperative: Through hepatic a. cannulae: ADR + lipiodol alone	Postoperative: Through hepatic a. cannulae: + IL-2	Postoperative: Through hepatic a. cannulae: + (LAK)	Postoperative: Through hepatic a. cannulae: + (CTL)	Multicentric occurrence
A	26	60.3 ± 8.0	22/4			I:16	0:20	0:25	Hr1 >	7							
						II:9	1:1	1:1	Hr1 ≦ < Hr2	10 (53.8%)	16 (61.5%)	8	7	9 (34.6%)	(2)	(2)	11/26 (42.3%)
						III:1	2:5	2:0	Hr2 ≦	9							
							3:0	3:0									
B	9	61.6 ± 9.6	7/2	Lung	6	I:6	0:4	0:1	Hr1 >	1							
				Bone	1	II:2	1:1	1:0	Hr1 ≦ < Hr2	2 (22.2%)	3 (33.3%)	4	2	1 (11.1%)	(1)	(2)	0/9 (0/%)
				Lymphnodes	1	III:1	2:2	2:1	Hr2 ≦	6							
				Diaphragm	1		3:2	3:0									

Clinical stage, the degree of accompanying liver dysfunction of the host of HCC; *Image V_P and V_V*, the extent of vascular invasion of the tumor judged by preoperative imaging diagnosis; *Hr1*, resection of one-segment; *Hr2*, resection of two-segments or one lobe; *+IL2*, continous IL2 infusion together with intermittent injections of ADR and lipiodol; *LAK*, lymphokine activated killer cell infusion to the hepatic artery; *CTL*, cytotoxic lymphocyte infusion into the hepatic artery; *TAE*, transcatheter arterial embolization (The numbers in parentheses below CTL and LAK represent the number of patients who received CTL or LAK therapy together with IL2 infusion.)

Table 1b. Clinical features of Stage IV HCC patients who underwent hepatic arterial cannulation

									Postoperative				
										Through hepatic a. cannulae			
	n	Age (mean ± SD)	Sex M/F	Metastasis	Clinical stage	Image V_P	Image V_V	TAE alone	ADR + lipiodol alone	+ IL-2	+ (LAK)	+ (CTL)
A	9	59.3 ± 13.2	7/2		I:4 II:4 III:1	0:0 1:3 2:4 3:2	0:5 1:3 2:0 3:1	0	5	4	0	0
B	2	61, 32	2/0	lung 1 skin 1	I:1 II:1 III:0	0:1 1:1 2:0 3:0	0:1 1:0 2:0 3:1	0	2	0	0	0

of patients: One is comprised of seven patients with stage IV-A and one patient with stage IV-B, who underwent reduction surgery of more than two segments and subsequent immunochemotherapy as described in Materials and Methods; and the other group is comprised of eight patients with stage I and II, who underwent curative resection[8] and had no remaining tumors.

Postoperative Treatment of the Remaining Tumors

Of the 35 patients who underwent reduction surgery, 2 died of liver failure within 1 month, 1 with stage IV-A, who was in clinical stage II and underwent lateral segmentectomy and ethanol injection, and another with stage IV-B who was in clinical stage III and underwent trisegmentectomy. The remaining 33 patients received various postoperative treatments for residual tumor cells (Table 1). During the early period, 12 patients received TAE alone every 6 months for remaining tumors. Chemoembolization, using 10 mg Adriamycin (ADR) (Kyowa Hakko, Japan) in 2 ml distilled water and 0.5 ml lipiodol, was performed through cannulae into the hepatic artery in 19 patients either once a week or every 2 weeks. Two patients who could not undergo hepatic arterial cannulation due to vascular anomalies in the remnant liver received hyperthermia and percutaneous ethanol injection.

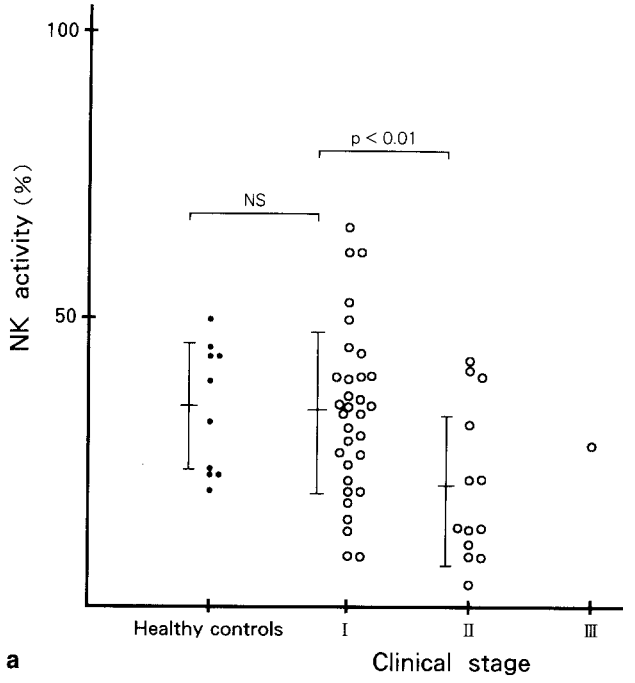
Adoptive immunotherapy, using recombinant interleukin-2 (r-IL2) as a basic immunomodulator,[10] was performed in ten patients, in the form of CTL infusion to the hepatic artery in four cases and lymphokine-activated killer cell (LAK)[11] infusion to the hepatic artery in three cases. For the CTL preparation, isolated tumor cells, which had been obtained by reduction surgery on that particular patient and preserved in the programmed freezer (Bio freezer, BF110 Tabai, Japan), were incubated with peripheral lymphocytes.[12] During 1989 and 1990, our postoperative hepatic arterial infusion regimen consisted of intermittent single injections of ADR, 10 mg/2 ml distilled water, starting 1 week after reduction surgery, with a continuous infusion of r-IL2 at 0.35×10^6 JRU/day (S-6820, Shionogi Pharmaceutical, Japan) through a subcutaneously implanted pump, commencing 2 weeks after reduction surgery.[13]

All clinical data are expressed as the means ± SD. Statistical analyses were performed by Student's *t*-test or the paired *t*-test.

Results

Clinical Features of the Stage IV HCC Patients who Underwent Liver Resection (Table 1)

The stage IV patients who underwent reduction surgery between 1985 and 1990 were mostly in clinical stage I or II[9] and had little portal or hepatic vein tumor invasion (V_{P_0} and V_{V_0}), as determined by pre- and perioperative imaging diagnoses. Two patients with stage IV-A and five with stage IV-B HCC had no accompanying liver cirrhosis. All the stage IV-A patients had multiple tumors in both lobes, while six of the stage IV-B patients had tumors only in one lobe. Lung metastases in the stage IV-B patients were limited to one lung. The maximum diameter of the largest tumors in the stage, IV-A patients were: >10 cm in 3 cases, 5–10 cm in 9 cases, and <5 cm in 14 cases; while in the stage IV-B patients there were 3, 4, and 2 cases in each group, respectively. Nineteen patients (54.3%), being 11 in stage IV-A and 8 in stage IV-B, had a removal rate of more than 80%, while 7 patients (20%), being 6 in stage IV-A and 1 in stage IV-B, had a removal rate of less than 50%. Eleven patients had no indications for liver resection and therefore received hepatic cannulation alone (Table 1b) for: Vascular invasion of the



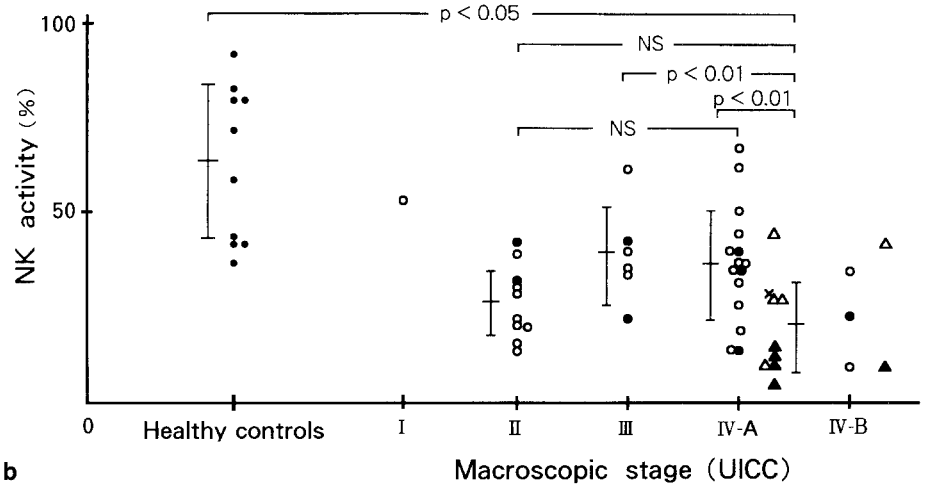


Fig. 1a,b. Comparison of preoperative natural killer (*NK*) activity in different **a** clinical and **b** UICC macroscopic stages. In Fig. 1b, *open circles* represent clinical stage I with liver resection; *closed circles* represent clinical stage II with liver resection; *open triangles* represent clinical stage I with hepatic arterial cannulation alone; *closed triangles* represent clinical stage II with hepatic arterial cannulation alone; *crosses* represent clinical stage III with hepatic arterial cannulation alone; and *dots* represent healthy controls. *NS*, not significantly different * $P < 0.05$

main trunk of the portal vein or inferior vena cava in 4 cases; a history of tumor rupture in 3 cases; clinical stage III in 1 case; renal failure in 1 case; and multiple distant organ metastases in 2 cases.

Multicentric Tumors in Stage IV HCC

Of the 26 stage IV-A patients who underwent reduction surgery, 11 (42%) had multicentrically occurring HCC, confirmed by histological analysis, although no such HCC was detected in the stage IV-B patients. No vascular tumor invasion was detected by preoperative US in any of these 11 stage IV-A patients.

Tumor-Bearing Host Immunity (Fig. 1)

The preoperative NK activity of 13 patients in clinical stage II (20.9 ± 13.5%) was significantly lower ($P < 0.01$) than that of 32 patients in clinical stage I (33.7 ± 14.6%) or the 10 healthy controls (33.0 ± 11.8%) (Fig. 1a). On the other hand, the NK activity of 15 macroscopic stage IV-A patients who underwent liver resection (36.3 ± 15.1%) was not significantly different from that of 10 patients in stage II (26.3 ± 9.3%) or 6 in stage III (38.8 ± 12.8%, $P > 0.05$), but was higher than that of 9 stage IV-A patients who were unable to undergo liver resection (19.2 ± 12.2%, $P < 0.01$) (Fig. 1b).

The postoperative changes in peripheral NK activity are shown in Fig. 2. In the stage IV patients who

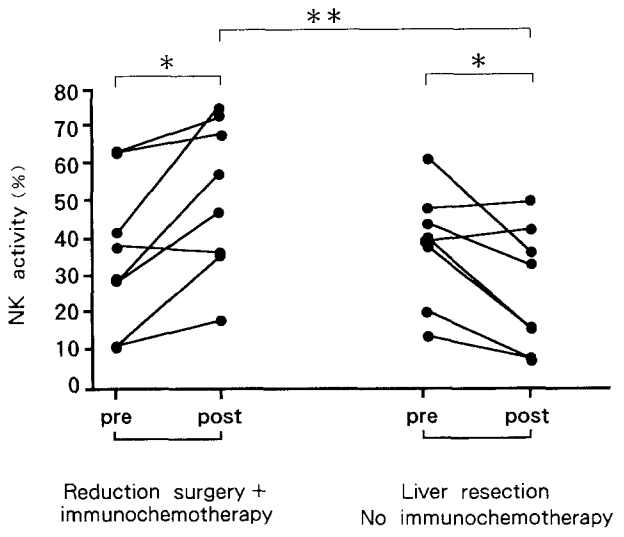


Fig. 2. Postoperative changes in peripheral NK activity. Data between the operation and induction of immunotherapy are not included. *Pre*, mean values between 0 and 2 months before surgery; *Post*, mean values between 2 and 4 months after surgery. * $P < 0.05$ by paired Student's t test; ** $P < 0.005$ by Student's t test

underwent liver resection and subsequent adoptive immunotherapy, NK activity increased postoperatively within 2 weeks after the induction of therapy and remained high for about 8–10 months.[13] On the other hand, in the patients who underwent liver resection without any subsequent immunotherapy, NK activity decreased after the operation and was significantly lower than that in the former patients, even 2–4 months after the operation.

Direct Effect of Postoperative Immunochemotherapy

In the ten patients who underwent reduction surgery and subsequent immunochemotherapy, comprised of nine with stage IV-A and one with stage IV-B HCC. Complete response (CR), being the complete disappearance of tumors for more than 4 weeks, was observed in two cases. Partial response (PR), being more than a 50% decrease lasting longer than 4 weeks in the diameters of all measurable lesions, was observed in three cases. No change (NC), being an objective response of less than 25% in all measurable lesions, was observed in three cases. Progressive disease (PD), being more than a 25% increase in the diameters of all measurable lesions or the appearance of new tumor, was observed in two cases, both of whom died of lung metastasis during the first 6 months.

Cumulative Survival Rate

The 2-year survival rate of the stage IV-A patients following reduction surgery was 49%, while that of the stage IV-B patients was 13% (Fig. 3). Six stage IV-A and one stage IV-B patient survived for more than 2 years. In fact, one of the stage IV-A patients, a 56-year-old male who had one large tumor 13 × 13 × 11 cm in size, in the right lobe and small nodules in both lobes, has survived for more than 4 years. He underwent right lobectomy and has received routine TAE every 6 months postoperatively. At present, his remaining liver contains multiple small tumors, but no extrahepatic metastases have been observed. The main tumor and resected satellite tumors were moderately differentiated HCC with a trabecular pattern and, although they could not be identified as multicentric occurrences by histological analysis, a thick capsule formation on the expansively growing main tumor suggested that it was slow growing. The resected specimens from the other five stage IV-A patients who survived for more than 2 years contained multicentrically occurring HCC, and none of these patients had any extrahepatic metastases for 2 years postoperatively. No patient who underwent liver resection of less than one segment survived longer than 2 years. Only one of the stage

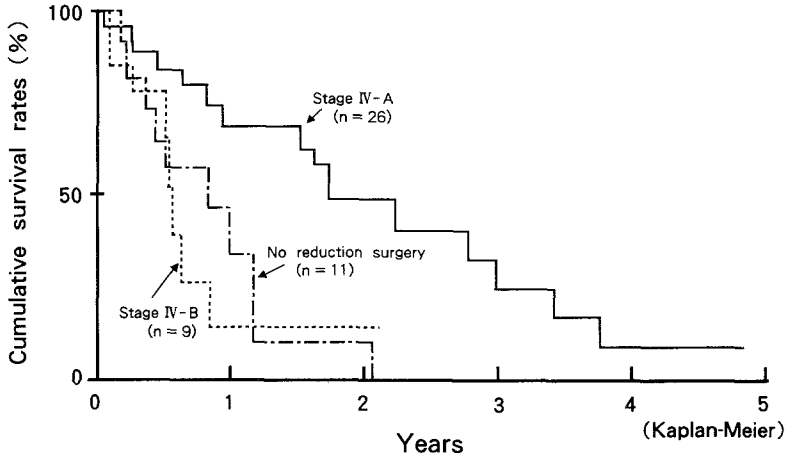


Fig. 3. Cumulative survival rates of stage IV-A and IV-B patients following reduction surgery, and of stage IV patients who received only hepatic arterial cannulation

IV-B patients survived more than 2 years, having received immunochemotherapy after extended right lobectomy and ethanol injection.

The stage IV patients who did not undergo reduction surgery, being nine with stage IV-A and two with stage IV-B, had a poor outcome compared with the stage IV-A patients who underwent reduction surgery. Two patients received immunochemotherapy, one of whom survived for 9 months and the other for 2 years. The remaining patients died within 1 year from cancer, this survival rate being similar to that of the stage IV-B patients who underwent reduction surgery.

Discussion

According to the UICC classification,[1] stage IV HCC is defined as grade A or B. Stage IV-A is defined by the T factor, T4, which denotes multiple tumors in more than one lobe, or tumors involving a major branch of the portal or hepatic veins. Stage IV-B HCC is defined as HCC with distant organ metastases, irrespective of the size of the primary liver tumor. However, we have experienced some stage IV-A HCC patients who responded favorably to anti-cancer therapy without developing vascular invasion or distant organ metastasis for relatively long periods, implying that there are different tumor characteristics even in stage IV-A HCC.

According to a recent analysis of intrahepatic multiple tumors,[5] the co-existence of multicentrically occurring HCC and intrahepatic metastatic HCC must be recognized in stage IV patients. In this study 42% of the stage IV-A patients had multicentric HCC, while there were no such cases among the stage IV-B patients. It seems possible that multicentric HCC may be found in some cases of stage IV-B HCC. However, their tumor progression seems to be so rapid that reduction surgery is less indicative.

No definite criterion for multicentrically occurring tumors has been established, except for hepatitis B virus (HBV) carriers, in whom a clonal analysis can be carried out by examining the integration patterns of HBV DNA in the nuclear DNA of each intrahepatic tumor.[14] The present criteria may not cover all of these tumors in an advanced stage. However, since HCC has a tendency to become less differentiated with an increase in size,[15] and because intrahepatic metastasis is rarely seen with well-differentiated HCC, well-differentiated tumors determined by the present criteria can be regarded as multicentrically occurring. Thus, surgical removal is recommended for large and main tumors which are relatively less differentiated and grow rapidly, followed by subsequent multidisciplinary treatment for any remaining tumors to improve prognosis.

Clinically, it is necessary to determine preoperatively whether there are clusters of slow-growing tumors in stage IV HCC, and to remove any rapidly growing tumors among them. The proliferation rate of the remaining tumors should then be suppressed by subsequent multidisciplinary treatment. It is still difficult to decide the operability of tumors in some cases, despite histological or DNA ploidy pattern analyses[16] following fine needle biopsy.[17] However, it is suggested that tumors with the following characteristics should be considered for reduction surgery: (1) main tumors occupying one lobe with small metastatic or multicentric nodules scattered in the remaining liver; and (2) those with no vascular invasion or distant organ metastasis.

To improve the survival rate of stage IV HCC patients, especially those with stage IV-B, the immunity of the tumor-bearing host as well as the characteristics of the tumor itself must be taken into consideration. Peripheral NK activity is an indicator of immunity[8,18] and its negative correlation with malignant status has been demonstrated.[18] In the present study, the NK activity of peripheral blood was significantly lower in clinical stage II than that in clinical stage I. According to our results, there is a tendency for liver dysfunction to reduce NK activity, although no data for clinical stage III were available. On the other hand, when the levels of NK activity were compared among the UICC macroscopic stages, they decreased only in the unresectable stage IV patients. Thus, low NK activity may indicate a combination of both lowered immunity status in very advanced malignancy and severe liver dysfunction, this conclusion being consistent with other analyses[19–22] in which depressed NK activity levels in HCC patients have been reported. In this study, postoperative NK activity was enhanced by immunotherapy even in patients with low preoperative NK activity, which suggests that certain stage IV patients can tolerate surgical insults if appropriate postoperative immunotherapy is given. Postoperative immunotherapy is very important because it can prevent a postoperative decrease in NK activity, which may continue for more than 4 weeks.[22]

In a previous study, we examined in vitro changes in peripheral lymphocyte subsets, incubated with IL2, from Stage IV HCC patients and healthy controls.[7] An immunosuppressive condition in advanced HCC patients was shown by a high ratio of suppressor to helper T-cell subsets[23] that was not modulated even in the presence of IL2. These results indicate that immunological stimuli which modify lymphocyte subsets, probably from the tumor itself, exist in advanced HCC patients. At this point, it would also be rational to implement procedures to reduce target tumor cells so that recovery from the immunosuppressive conditions that occur in advanced HCC patients may be induced.

We previously demonstrated the effects of infusing ADR and r-IL2 into the hepatic artery for advanced HCC.[13] In this study, after the induction of immunochemotherapy the levels of NK and LAK activity increased and were maintained at high levels for 8 to 10 months. During this period, direct effects on liver tumors and metastatic lesions were observed, although the NK and LAK levels decreased later, and their effects on metastatic lesions were reduced. Thus, in order to further improve the survival rate of patients with stage IV HCC, especially those with stage IV-B, more effective immunotherapy is necessary.

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